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Original Communications

DETERMINATION OF BONE AGE IN CHILDREN

A METHOD BASED ON A STUDY OF 1,129 WHITE CHILDREN

LOUIS A. LURIE, M.D., SOL LEVY, M.D., AND MAX L. LURIE
CINCINNATI, OHIO

MANY elaborate treatises and monographs[1-3] have been written on osseous growth and the determination of skeletal age. Unfortunately, most of these reports are too complicated and involved to meet the needs of the busy pediatrician, endocrinologist, and child psychiatrist. Many physicians have stressed the need for a method for determining bone age that would entail the least amount of expense to the patient and at the same time be both accurate and simple.

The present report is an attempt to present a practical and inexpensive method for determining skeletal age in children. It is based on an analysis of data obtained at the Child Guidance Home.

Every child admitted for observation at the Child Guidance Home is carefully studied from the endocrine standpoint. In connection with this study, roentgenograms of the centers of ossification are made routinely on every child. As a result, it is possible to determine the skeletal or bone age of the child and to compare it with his chronological age.

As aptly expressed by Buehl and Pyle,[4] "The concept of skeletal age is based on an aggregate of multiple maturity determinators." The determinators most frequently used at the Child Guidance Home are roentgenograms of the hand and wrist, the elbow, the shoulder, the pelvis, and the foot and ankle.

In connection with this study, the roentgenograms of more than 2,100 white children were examined. Of this number, only 1,129 were used, the remainder being excluded because they were found to be roentgenograms of children suffering from various endocrine disorders or from marked nutritional disturbances.

Of the 1,129 children in this series, 704 were boys and 425 were girls. Their ages ranged from 2½ to 19 years.

From the Child Guidance Home of the Jewish Hospital.

Children's Behavior Problems. Vol. II. Relative Importance and Interrelations Among Traits. Luton Ackerson, University of Chicago Press, 1942, Chicago, 570 pages. Price, $5.

A statistical study based on the case records of the Illinois Institute for Juvenile Research. Volume I, which considered genetic and intellectual factors, was published in 1931. Volume II reports a study of the intercorrelation of certain behavior traits chosen because of their frequency of occurrence in the case records of the Institute. The monograph, because of its nature, is of more interest to the child psychologist than to the pediatrician.

Synopsis of Diseases of the Skin, Richard L. Sutton, M.D., and Richard L. Sutton, Jr., M.D., The C. V. Mosby Company, St. Louis, 1942, 481 pages with 413 illustrations. Price, $5.50.

A handy desk manual on skin diseases. The material is arranged in the usual textbook manner. The text is good and the illustrations excellent. The book is of particular value to the practitioner of pediatrics for quick reference to the causes and treatment of the more unusual skin conditions which are occasionally encountered.

Child Behavior and Development. Edited by Roger Baker, James S. Kounin, and Herbert F. Wright, McGraw-Hill Book Co., Inc., New York, 1943, 652 pages. Price, $4.

The volume aims to provide material for work in child psychology. The editors have selected twenty-five studies suggested by fifty-two members of the Society for Research in Child Development. The studies have been abstracted or adapted from studies by the leaders in child psychology. The material selected covers a very wide field and includes such subjects as development of the newborn and young infant, twins, gifted children, intelligence measurements, children's fears, play social behavior, adolescent personality, etc. Although the volume is intended for college students, it can be read with great profit by the pediatrician as it will give him the background of much research and the methods of research being done by the child psychologist. The selection of material is excellent.

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As aptly expressed by Buehl and Pyle,[4] "The concept of skeletal age is based on an aggregate of multiple maturity determinators." The determinators most frequently used at the Child Guidance Home are roentgenograms of the hand and wrist, the elbow, the shoulder, the pelvis, and the foot and ankle.

In connection with this study, the roentgenograms of more than 2,100 white children were examined. Of this number, only 1,129 were used, the remainder being excluded because they were found to be roentgenograms of children suffering from various endocrine disorders or from marked nutritional disturbances.

Of the 1,129 children in this series, 704 were boys and 425 were girls. Their ages ranged from 2½ to 19 years.

From the Child Guidance Home of the Jewish Hospital.

At first the children were divided into groups on a basis of one-half-year age differences. This method was soon discarded because the differences in the findings were not great enough to be of practical value. The final grouping was made on a basis of one-year age differences.

Each child's roentgenograms were read from the standpoint of the time of appearance of the various epiphyses (bone centers) as well as from the standpoint of the time of their fusion. With but few exceptions there was a varying range of time during which the individual bone centers appeared and fused. For example, the distal epiphysis of the ulna was found to be present in some children (boys) as early as 5 years of age, but at 10 years it was present in every child. Similarly, this epiphysis in boys began to fuse at 14 years of age in a few instances, but was first fused in every child at 18 years of age. The reason for the apparent lack of spread in onset of some of the epiphyses was because the ages of the children in our series began at 2½ years. For example, we found all the epiphyses of the metacarpals and phalanges to be present at 2½ years. However, it is well known that some of these appear long before this time; in fact, may be present at birth.

Because of these findings, charts were made showing the range of the age distribution of all the bone centers, both in regard to the time of their appearance and the time of their fusion. Furthermore, since we, like all other workers in this field, found that girls showed an accelerated bone maturation, separate charts were made for boys and girls.

In order to make this procedure as simple and as inexpensive as possible without, at the same time, sacrificing accuracy, only four roentgenograms were used; namely (1) the hand, including the wrist; (2) the elbow; (3) the pelvis; and (4) the foot, including the ankle. Charts 1 to 17 represent the range of time of the appearance and fusion of the epiphyses that were used in obtaining the data for this study.

In Charts 1 to 17 the shaded columns represent boys and the unshaded columns represent girls.

Chart 2, which represents the data on the time of the appearance and fusion of the distal epiphysis of the ulna, is typical of the entire group. From this chart it will be seen that the distal epiphysis of the ulna begins to appear in girls at the age of 4 years (8 per cent of the children at that age) and in boys, at the age of 5 years (22 per cent at that age) and is present in all the girls at the age of 8 and in all the boys at the age of 10 years. Similarly, this epiphysis begins to fuse at the age of 12 years in girls (4 per cent at that age) and at the age of 14 years in boys (3 per cent at that age). It is first fused in all girls at the age of 17 and in all the boys at the age of 18 years. It will also be noted from this chart that this epiphysis appears in the majority of the cases of girls from 6 years (69 per cent) to 8 years (100 per cent), while in the cases of the boys it appears in the bulk of the cases from 7 years

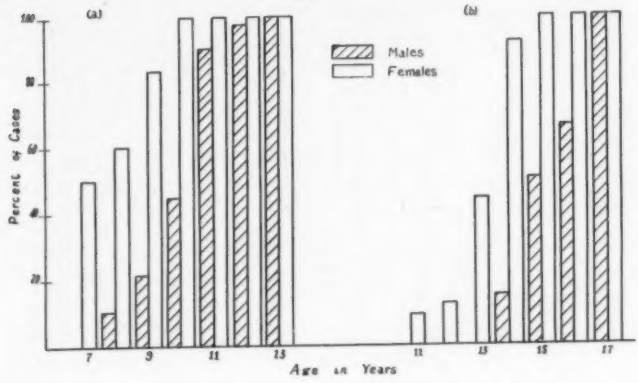

Chart 1.—Range in time of (*a*) appearance and (*b*) fusion of the olecranon process of the ulna.

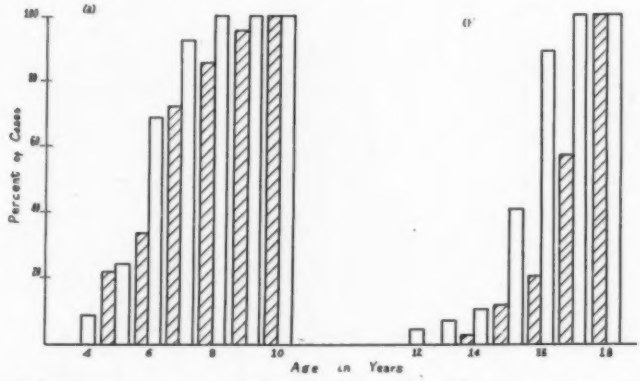

Chart 2.—Range in time of (*a*) appearance and (*b*) fusion of the distal epiphysis of the ulna.

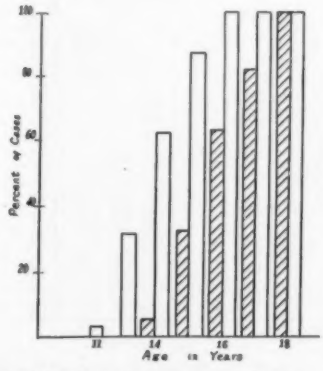

Chart 3.—Range in time of fusion of the epiphyses of the phalanges.

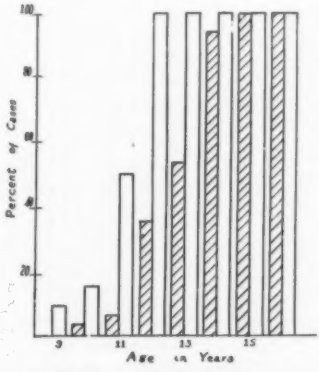

Chart 4.—Range in time of appearance of the sesamoid bone of the thumb.

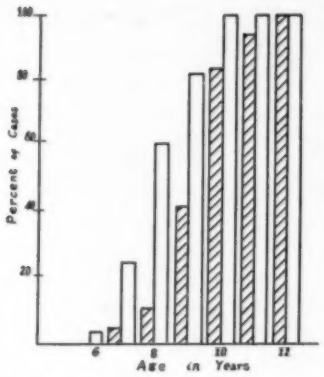

Chart 5.—Range in time of appearance of the styloid process of the ulna.

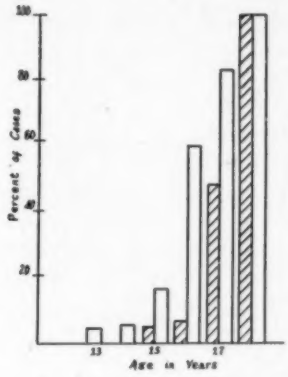

Chart 6.—Range in time of fusion of the distal epiphysis of the radius.

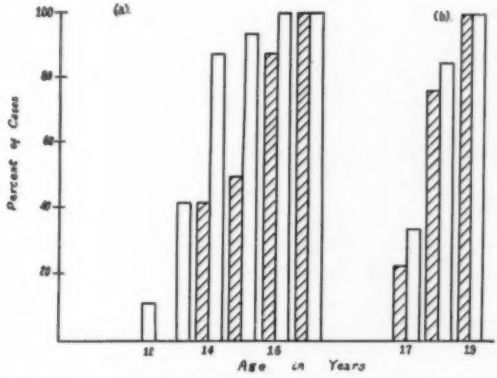

Chart 7.—Range in time of (*a*) appearance and (*b*) fusion of the crest of the ilium.

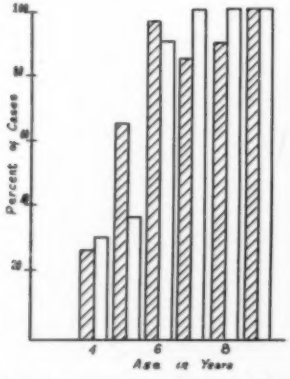

Chart 8.—Range in time of fusion of the rami of the os pubis.

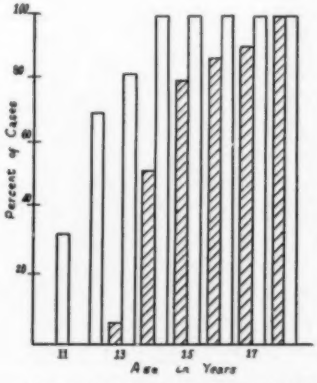

Chart 9.—Range in time of fusion of the acetabulum.

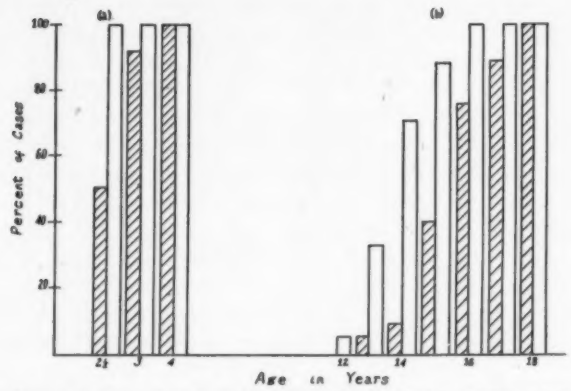

Chart 10.—Range in time of (*a*) appearance and (*b*) fusion of the epiphyses of the metacarpals.

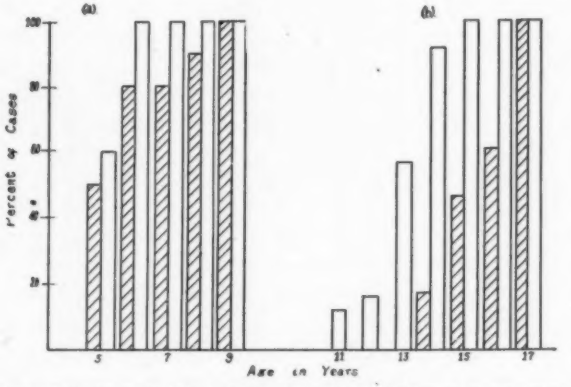

Chart 11.—Range in time of (*a*) appearance and (*b*) fusion of the proximal epiphysis of the radius.

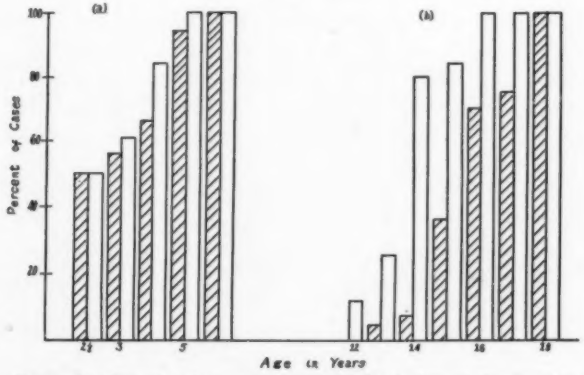

Chart 12.—Range in time of (*a*) appearance and (*b*) fusion of the greater trochanter of the femur.

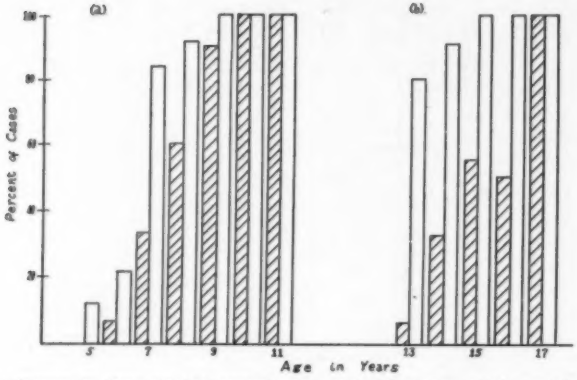

Chart 13.—Range in time of (*a*) appearance and (*b*) fusion of the epiphysis of the os calcis.

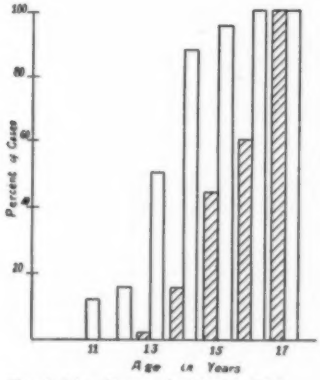

Chart 14.—Range in time of fusion of the medial epicondyle of the humerus.

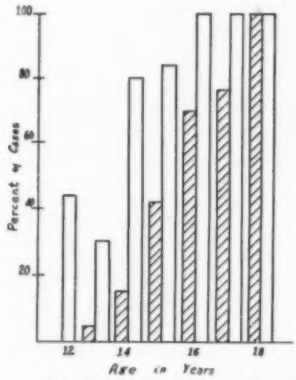

Chart 15.—Range in time of fusion of the head of the femur.

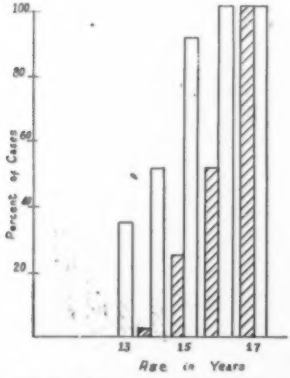

Chart 16.—Range in time of fusion of the distal epiphyses of the tibia and fibula.

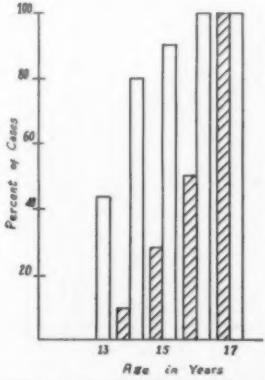

Chart 17.—Range in time of fusion of the epiphyses of the metatarsals.

(72 per cent) to 10 years (100 per cent). Similarly, fusion of this epiphysis occurs in girls principally between the ages of 16 years (88 per cent) and 17 years (100 per cent), and in boys, between 17 years (56 per cent) and 18 years (100 per cent). The instances of the earlier appearance of this epiphysis as well as its earlier fusion represent extremes and hence are relatively unimportant.

In certain instances only the appearance of an ossification center such as the sesamoid bone of the thumb (Chart 4) or the fusion of a center of ossification such as the acetabulum (Chart 9) is described. The reasons for this are obvious.

Fig. 1 for boys and Fig. 2 for girls present in graphic form the summary of the data shown in Charts 1 to 17. The entire spread in the time of appearance and fusion of each center of ossification is graphically shown by a horizontal line. The broken part of this line represents the appearance of the centers of ossification in less than 50 per cent of the children for those age groups, while the solid line represents the appearance of the center in more than 50 per cent of the children for those age groups. The single dot or the dot at the end of the solid line represents the age at which the epiphysis or center of ossification is either present or fused in 100 per cent of the children at that age.

Hence, by using these two graphs (Figs. 1 and 2) it is possible to determine quickly what should be found on a roentgenographic examination of the bone centers of a normal child at a given age. For example, to determine what bone centers or maturity determinators should be present at a given age, it is only necessary to follow the vertical line at that age—any dot that this line intersects as well as all the dots to its left represent bone centers which should be present or fused at that age. All solid lines touched by this vertical line represent epiphyses likely to be present or fused, while the broken lines touched by the vertical line represent epiphyses only infrequently present or fused at that age.

Specifically, in the case of a 5-year-old girl, the following bone centers should be present: epiphyses of metacarpals and phalanges, head of femur, epiphyses of metatarsals, all the tarsal bones, distal epiphyses of tibia, fibula, and radius, medial epicondyle of the humerus, all the carpal bones, and the greater trochanter, in the order named. The proximal epiphysis of the radius is likely to be present. The rami of the os pubis are infrequently fused at this age. The distal epiphysis of the ulna and epiphysis of the os calcis are also infrequently present (Fig. 2).

Similarly, in the case of a boy aged 17, all the bone centers should be present and in addition, the following fusions should have occurred: the distal epiphyses of the tibia and fibula, the epiphyses of the metatarsals, the medial epicondyle of the humerus, the proximal epiphysis of the radius, the rami of the os pubis, the epiphysis of the os calcis, and the olecranon process of the ulna. All the other centers are likely to

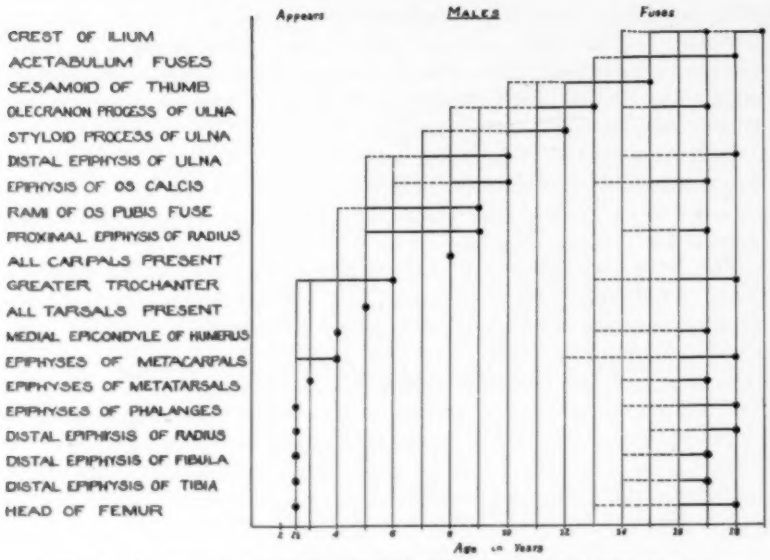

Fig. 1.—Appearance and fusion of bone centers at various ages in boys.

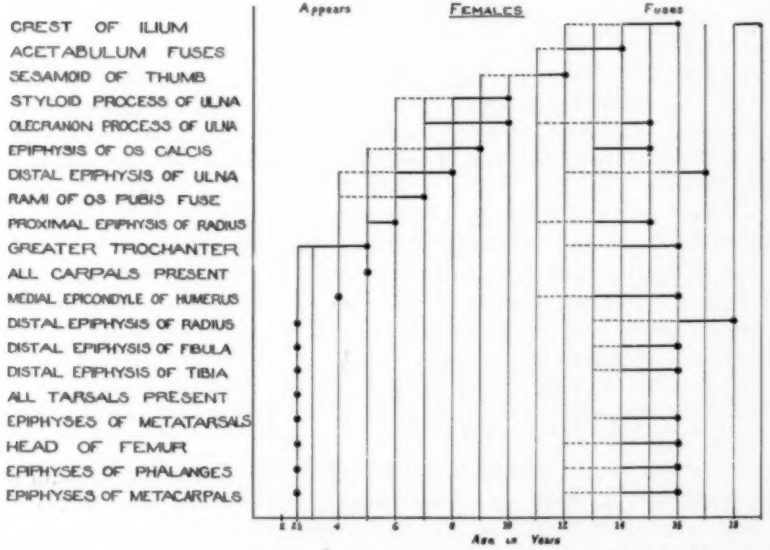

Fig. 2.—Appearance and fusion of bone centers at various ages in girls.

be fused with the exception of the crest of the ilium which is only infrequently found to be fused at this age (Fig. 1).

In other words, if the roentgenograms show conditions other than those enumerated above, then it can be concluded that one is dealing with a case of abnormal bone growth or development (either delayed or accelerated).

TABLE I

AGE, IN YEARS, OF 100 PER CENT APPEARANCE AND FUSION OF THE VARIOUS BONE CENTERS USED IN THIS STUDY

MALE		BONE CENTERS	FEMALE	
APPEARANCE	FUSION		APPEARANCE	FUSION
		A. *X-rays of hand, including wrist*		
8	–	All carpal bones	5	–
4	18	Epiphyses of metacarpals	2½*	16
2½*	18	Epiphyses of phalanges	2½*	16
2½*	18	Distal epiphysis of radius	2½*	18
10	18	Distal epiphysis of ulna	8	17
12	–	Styloid process of ulna	10	–
15	–	Sesamoid bone of thumb	12	–
		B. *X-rays of elbow*		
13	17	Olecranon process of ulna	10	15
9	17	Proximal epiphysis of radius	6	15
4	17	Medial epicondyle of humerus	4	16
		C. *X-rays of pelvis*		
–	9	Rami of os pubis	–	7
2½*	18	Head of femur	2½*	16
6	18	Greater trochanter of femur	5	16
–	18	Acetabulum	–	14
17	19	Crest of ilium	16	19
		D. *X-rays of foot, including ankle*		
5	–	All tarsal bones	2½*	–
3	17	Epiphyses of metatarsals	2½*	16
10	17	Epiphysis of os calcis	9	15
2½*	17	Distal epiphysis of tibia	2½*	16
2½*	17	Distal epiphysis of fibula	2½*	16

*These bone centers may be present in 100 per cent of the cases much earlier. Our series of cases began with the age of 2½ years.

Table I shows in tabular form the ages of boys and girls at which the appearance or fusion of the different centers of ossification occurs in each case. This table is arranged in accordance with the findings in each of the four x-ray plates used in the examination of every child.

The data from Figs. 1 and 2 primarily provide criteria for determining normal bone age. However, by comparing the bone age of the child with his chronological age, the bone quotient can be easily computed. For example, if a child of 10 years is found to have a bone age of 8 years, his bone quotient, or B. Q., can be stated to be 80 per cent of the normal. This is derived by dividing the bone age by the chronological age. Similarly if a child of 10 years is found to have a bone age of 12 years, his bone quotient is 120 per cent. Since the bone age is determined on the basis of one-year variation, the same must hold true for the chronological age. Hence, a variation of six months or more is considered an additional year, while less than six months is discarded. In this way a uniform method of deviations from the norm in the rate of

bone development becomes available. This determination in many respects is comparable to the intelligence quotient and the social quotient determinations used to describe the degree of intellectual and social maturation. Its value becomes demonstrable in diagnosing certain metabolic and endocrine disorders and also in furnishing a uniform basis for statistical studies and analyses.

CONCLUSIONS

From the data derived from this series of cases, the following conclusions may be drawn:

1. Four roentgenograms, namely (1) the hand, including the wrist, (2) the elbow, (3) the pelvis, and (4) the foot, including the ankle, are adequate for determining the bone age of a child.

2. The lesser trochanter of the femur should be disregarded as a bone age determinator because of the likelihood of distortions due to variations in the focusing on this part.

3. The variations in the state of osseous development based on one-half-year age differences were found to be negligible for all practical purposes.

4. Girls showed a definite acceleration in their bone growth or development as compared to boys.

5. Figs. 1 and 2 provide a quick and simple method to determine bone age in boys and girls, respectively.

6. A new term, bone quotient (B.Q.), is introduced and its value explained.

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FEET OF NORMAL CHILDREN

A Study of Lateral X-rays of the Weight-Bearing Foot

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Margaret Anderson, M.S.P.H.
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A PART of the Fels Institute's longitudinal study of individual developmental differences in a group of normal children is a study of children's feet. We shall present here the results of only one approach, a study of lateral x-rays of the weight-bearing foot.

MATERIAL AND METHODS

For the last four and one-half years we have taken lateral x-rays of the left foot with the child in standing position. Such x-rays have been taken at intervals of six months. The ages of these children ranged from 2½ to 13 years. Each child has had from one to nine x-rays. Over 800 x-rays have been studied.

A standard x-ray technique is carefully maintained. The child stands symmetrically with its weight distributed equally on both feet. The target-film distance is 36 inches (91.5 cm.). The central ray is directed at the external malleolus. The cassette is placed between the feet, close to the left foot but not in contact with it (it should not brace the internal malleolus). A film of sufficient size is chosen to include the entire foot and half of the calf (Fig. 1).

These x-rays have been analyzed according to a method described by Bertani and Moreau.[1] These authors have measured four angles defined by the following landmarks (Figs. 2 and 3):

1. The lowest point of the head of the talus.
2. The lowest point of the calcaneus.
3. The lowest point of the head of the first metatarsal.
4. The lowest point of the base of the first metatarsal.
5. The lowest point of the calcaneus at the calcaneocuboid articulation.
6. The lowest point of the head of the fifth metatarsal.

The angles *A* and *C* measure the height of the medial and lateral aspects, respectively, of the longitudinal arch. Angle *B* measures the anterior medial part of the arch, angle *D* the inclination of the calcaneus with the horizontal.

Slightly different landmarks must be selected in the younger children because the contours of the ossification centers differ somewhat from the final shape of the bones. In small children the ends of the metatarsal shafts have to be used instead of the heads. Also the position of points *2* and *5* may shift somewhat with age.

From the Samuel S. Fels Research Institute, Antioch College.

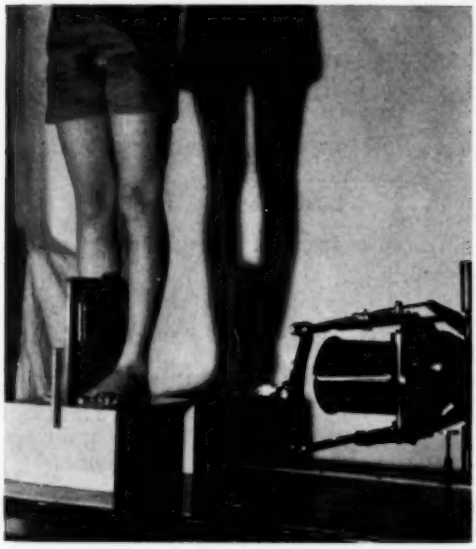

Fig. 1.—Shows x-ray tube, cassette, and foot in position for taking x-ray. Target-film distance is 36 inches, wiht tube centered at external malleolus and perpendicular to film.

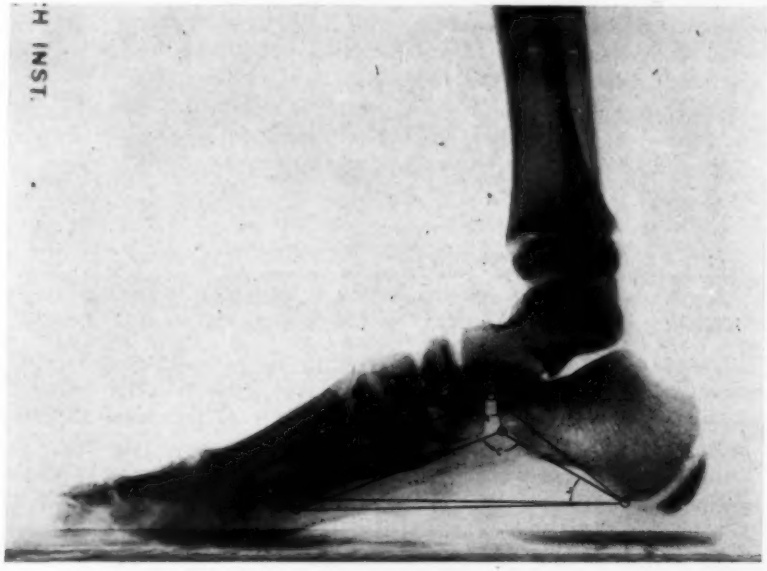

Fig. 2.—Reproduction of x-ray with angles marked; a high arch. Angle *A*, 119.0 degrees; *B*, 20.5 degrees; *C*, 129.0 degrees; *D*, 31.0 degrees.

The landmarks were designated by pinpricks on the film and the angles were measured with a goniometer. Once the landmarks were fixed in this manner, independent measurements rarely differed by more than one degree.

Fig. 3.—Reproduction of x-ray with angles marked; a low arch. Angle *A*, 147.5 degrees; *B*, 6.0 degrees; *C*, 144.0 degrees; *D*, 21.0 degrees.

Measurements on x-rays taken one year apart have been correlated (Table I). The high positive correlation coefficients indicate not only that the angles of individual feet are remarkably constant, but also that no major errors are introduced by variations of landmarks (see above), inconsistency of x-ray technique, measurements, etc. The somewhat lower values in the younger children are to be expected since in younger children the bone contours (and consequently the landmarks) change more rapidly and because the younger children do not follow instructions during the x-ray procedure as well as the older ones.

TABLE I

CORRELATIONS BETWEEN MEASUREMENTS OF FOOT ANGLES AT SUCCESSIVE AGES

AGES	ANGLE				NUMBER OF CASES
	A	B	C	D	
4 and 5 years	.83	.47	.68	.75	21
5 and 6 years	.87	.64	.79	.88	21
6 and 7 years	.65	.70	.88	.81	33
7 and 8 years	.89	.87	.95	.93	33
8 and 9 years	.89	.90	.96	.95	24
9 and 10 years	.92	.84	.93	.94	24

RELATIONSHIPS BETWEEN THE ANGLES

We have intercorrelated the four angles at three different age levels (Table II). The direction of the correlations is uniform, but for some unexplained reason most correlation coefficients were lowest at 6 years of age.

TABLE II

INTERCORRELATIONS OF FOOT ANGLES

	ANGLE								
	A			B			C		
	3 YR.	6 YR.	10 YR.	3 YR.	6 YR.	10 YR.	3 YR.	6 YR.	10 YR.
B	−.80	−.57	−.71						
C	.72	.50	.74	−.57	−.28	−.71			
D	−.79	−.57	−.78	.58	.28	.70	−.97	−.97	−.97

3 yr. N, 40.
6 yr. N, 55.
10 yr. N, 31.

C and *D* correlate very highly at all age levels (as might be expected since the landmarks forming the two angles are the same). In fact, the correlation is so high that it seems advisable to measure only one of these angles in the future. The correlations between the other angles are fairly high but sufficiently different from unity to justify their separate measurement.

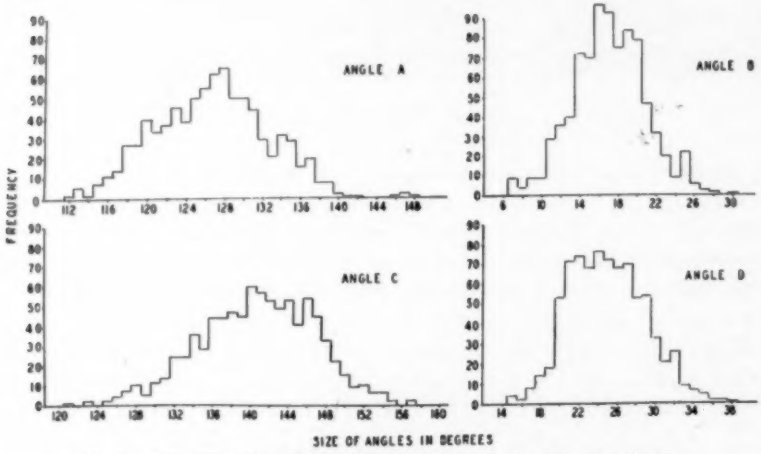

Fig. 4.—Frequency distributions for angles *A*, *B*, *C*, and *D*; all ages.

NORMS AND RANGE OF VARIATION

Frequency distributions at each age level closely approximate normal curves. Distributions of the four angles for the entire group are presented in Fig. 4.

How should this finding be interpreted? The normal frequency distributions seem to argue that, at least in our group, high as well as

low arches are normal variations. There is no group of cases which obviously exceeds the range of normal variation (as for instance, the blood sugar in diabetes or the blood pressure in hypertension). This is interesting and significant from the biometric point of view but is rather irrelevant for the physician because it does not mean that all arches are adequate to stand the strain to which they are exposed.

The next step was the calculation of means and standard deviations for succeeding age levels. Combined means for girls and boys are shown in Table III and Fig. 5. Separate means for girls and boys were calculated at 3, 6, 8, and 10 years of age and showed no significant differences for angle *A*, *C*, or *D*. Angle *B* showed no difference at 3 years, but at 6, 8, and 10 years it was significantly smaller for girls, as judged by the critical ratio criterion. The values for angle *B*, in degrees, are as follows:

AGE	GIRLS	BOYS	CRITICAL RATIO
3 yr.	19.0	19.0	0
6 yr.	16.6	19.7	3.7
8 yr.	15.6	17.8	2.6
10 yr.	13.6	16.0	2.2

Fig. 5 shows the trend of each angle with age. By inspection, angle *A* is seen to show no significant change. Angle *B* becomes gradually more acute after the age of 4 years. That this is a significant shift is indicated by a critical ratio of 4.9 for angle *B* at 4 and 11 years. However, this trend is probably not due to structural changes of the arch but to a change of landmarks. The base of the first metatarsal gradually changes its shape and extends to a lower level as ossification progresses. Angle *C* shows the lowest value at 6 years. However, the critical ratio for angle *C* at 6 and 10 years is 1.6, which cannot be considered significant. The reverse trend, also insignificant, with the highest value for angle *D* at 6 years is, of course, seen, since angles *C* and *D* utilize the same landmarks and as the one increases the other necessarily decreases.

The remarkably small age changes of the arch are interesting. They show that the arch is well developed relatively early in life. This fact has not always been appreciated. Footprints of young children give the erroneous impression that the arch develops only very gradually.

Bertani and Moreau[1] state that in the normal foot (of the adult) angle *A* should not be greater than 128 degrees; angle *B* should not be less than 14 degrees; angle *C* should not be greater than 150 degrees; angle *D* should not be less than 20 degrees.

These authors do not explain how they arrived at these normal limits, but it seems reasonable to assume that they used clinical criteria. Such clinical criteria are useful in adults in whom low arches usually, high

arches frequently, produce symptoms. This is not true for children. Children rarely complain of painful feet. We feel that it would be safer to use a biometric than a clinical criterion in children. We shall tentatively call "normal" all cases having angles within plus-minus one standard deviation (68.3 per cent), reserve judgment on those between plus-minus one and two standard deviations (27.2 per cent), and call

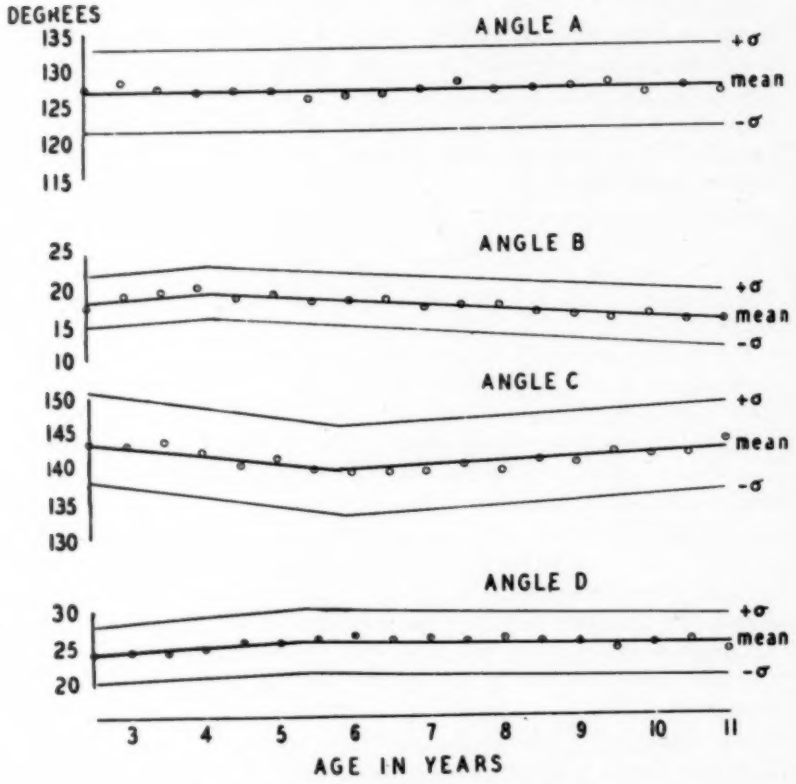

Fig. 5.—Age trends of angles *A*, *B*, *C*, and *D*.

"abnormal" those beyond plus-minus two standard deviations (4.5 per cent). Discrepancies between our standards (Table III) and those of Bertani and Moreau are seen for angles *A* (all cases) and *B* (older children only). The reason for these discrepancies cannot now be determined. We hope that we can follow our group of children long enough to find out which type of foot will eventually prove inadequate.

TABLE III

NORMAL RANGE OF FOOT ANGLES IN DEGREES (MEAN ± 1 SIGMA)

NUMBER OF CASES	AGE YR.	ANGLE			
		A	B	C	D
24	2½	121.5 to 133.5	14.5 to 20.5	137.5 to 149.5	20.0 to 28.0
40	3	121.5 to 135.5	15.5 to 22.5	137.0 to 149.0	20.0 to 28.0
44	3½	121.0 to 134.0	16.0 to 23.0	138.0 to 149.0	20.0 to 28.0
43	4	120.5 to 133.5	16.0 to 24.0	136.5 to 147.5	20.5 to 28.5
39	4½	120.5 to 133.5	15.5 to 21.5	133.5 to 146.5	21.0 to 30.0
43	5	121.0 to 133.0	16.0 to 22.0	135.5 to 146.5	21.5 to 29.5
50	5½	120.5 to 131.5	14.5 to 21.5	133.0 to 146.0	21.5 to 30.5
52	6	121.5 to 131.5	14.5 to 21.5	133.0 to 145.0	22.5 to 30.5
40	6½	121.5 to 131.5	14.0 to 22.0	133.5 to 144.5	22.5 to 29.5
42	7	121.0 to 133.0	13.5 to 20.5	133.5 to 144.5	22.0 to 30.0
36	7½	122.5 to 133.5	13.5 to 20.5	134.0 to 146.0	21.5 to 29.5
60	8	121.5 to 132.5	13.5 to 20.5	133.0 to 145.0	22.0 to 30.0
38	8½	121.5 to 132.5	13.0 to 19.0	134.0 to 147.0	21.5 to 29.5
35	9	121.0 to 133.0	12.5 to 18.5	135.0 to 145.0	22.0 to 29.0
29	9½	122.0 to 133.0	12.0 to 18.0	135.5 to 147.5	20.5 to 28.5
29	10	121.0 to 131.0	12.5 to 18.5	136.0 to 146.0	22.0 to 28.0
23	10½	121.5 to 132.5	11.5 to 17.5	135.5 to 146.5	22.0 to 29.0
16	11	120.0 to 132.0	11.0 to 18.0	138.0 to 148.0	21.0 to 27.0
683	All Ages	121.5 to 132.5	13.5 to 20.5	135.0 to 147.0	21.0 to 29.0

THE EFFECT OF LOAD CHANGES ON THE ARCH

X-rays of the left foot with weight distribution as indicated gave the following results in two children with high and low arches, respectively:

	ANGLE (DEGREES)			
J. M. (AGE, 7½ YR.)	A	B	C	D
Equal weight on both feet	116.0	21.5	136.0	28.0
All weight on left foot	115.5	21.0	135.5	28.0
All weight on right foot	112.0	24.0	133.5	31.0
S. T. (AGE, 5½ YR.)				
Equal weight on both feet	135.0	14.0	140.0	24.5
All weight on left foot	134.0	14.0	141.0	23.5
All weight on right foot	132.5	18.5	138.5	26.5

The results are interesting. Removing all the load had the expected effect of making the arch higher, but doubling the load had no appreciable effect on the angles.

In another experiment the main load was shifted to the anterior part of the foot. This was accomplished by combined flexion of the knees and upper foot joints. The following results were obtained:

	ANGLE (DEGREES)			
M. N. (AGE, 6 YR.)	A	B	C	D
Normal position	116.5	19.0	131.5	32.5
Weight shifted forward	122.0	15.5	133.5	32.0
M. K. B. (AGE, 9 YR.)				
Normal position	131.0	9.0	144.0	22.5
Weight shifted forward	135.0	7.0	149.5	19.5

The effect of this procedure is a distinct flattening of the arch. These results seem to confirm the contention of Jones,[2] that the stress on the longitudinal arch is proportional to the weight borne on the ball of the foot.

CORRELATIONS BETWEEN FOOT ANGLES AND SOME OTHER VARIABLES

The following conditions seemed most likely to be correlated with flat feet: overweight, knock-knees, and pronation.

The common association of flat feet with obesity is well known. The combination of flat feet and pronation has been mentioned by various authors.[3, 4] Some authors claim that flat feet are always pronated. Finally, knock-knees may be expected to aggravate both flat feet and pronation by transmitting the major portion of the body weight to the medial border of the foot.

We have correlated at three age levels the angles *A*, *B*, and *C* with weight: length ratios and with ratings of knock-knees and pronation (Table IV). The ratings were obtained from rear view photographs of the children in standard position.[5] Since the number of cases at the individual age levels is small, and since angle *A* shows no change with age, we also correlated this angle with knock-knees and with pronation, using 100 children ranging in age from 3 to 11 years. The correlation coefficient obtained for angle *A* with pronation is .32, while for angle *A* with knockknees it is .14, giving us nothing more significant than the findings shown in Table IV.

TABLE IV

CORRELATIONS BETWEEN FOOT ANGLES AND WEIGHT:LENGTH RATIO, KNOCK-KNEES, AND PRONATION

	ANGLE								
	A			B			C		
	3 YR.	6 YR.	10 YR.	3 YR.	6 YR.	10 YR.	3 YR.	6 YR.	10 YR.
Weight:length ratio[1]	.08	−.05	.40	.06	.12	−.28	.26	−.28	.27
Knock-knees[2]	.23	.35	.33	−.11	−.10	−.15	.42	.04	.13
Pronation[3]	.12	.56	.19	−.13	−.24	.02	.22	−.07	−.03

[1]Number of cases: 38 at 3 yr.; 55 at 6 yr.; 31 at 10 yr.
[2]Number of cases: 17 at 3 yr.; 18 at 6 yr.; 21 at 10 yr.
[3]Number of cases: 14 at 3 yr.; 18 at 6 yr.; 22 at 10 yr.

It is evident that all coefficients are low, many of them insignificant. However, all of the coefficients above .20 are in the expected direction. The coefficients of the foot angles with the weight: length ratio appear significant at 10 years but not at 3 and 6 years. This is probably due to the fact that overweight is fairly common at 10 years of age but so rare at 3 and 6 years that no significant correlation can be expected. We shall attempt no further explanation of the coefficients because of the small number of cases. Even lower and unquestionably insignificant correlations were obtained when the foot angles were correlated with some other posture variables, as hyperextension of knees and two different aspects of back posture. No correlation was obtained between

angle *A* and the age at which the children began to walk ($r = -.16$). This correlation was done because it was believed at one time that very early walking may produce or aggravate flat feet. Neither was rickets involved in causing flat feet. Only one or two of the children had, during infancy, x-ray signs suggestive of mild rickets. None had clinical rickets.

The important fact seems to be that all these correlations are low. It suggests that the height of the arch in children is not much affected by such obvious factors as presented themselves to us. This is compatible with the idea that differences in children's arches are largely determined by genetic factors. It seems not unlikely that the configuration of the arch in adults is much more dependent on environmental factors.

We investigated the possibility of genetic factors by the method of intersibling correlation. Using angle *A* we obtained a correlation of $.41 \pm .12$. This strongly suggests an hereditary factor, although this method does not give any information on the mode of inheritance. Kuhns[6] has stated that heredity appears to play a part in causing the so-called congenital flatfoot and has quoted evidence of a limited nature suggesting that it behaves like a recessive trait.

SUMMARY AND CONCLUSIONS

A study of the arches of normal children is presented. More than 800 lateral x-rays of weight-bearing feet were analyzed.

An analysis of certain angles measured showed that:

1. The method of measurement advocated by Bertani and Moreau can be applied to children over 2½ years of age and yields useful and reliable results.

2. Frequency distributions of these angles closely resemble normal curves.

3. Most children's arches show very little change with age.

4. Low arches appear to be correlated with weight:length ratio at older ages studied. Correlations of questionable significance were obtained between foot angles and pronation, knock-knees, some other postural variables and with age of starting to walk.

5. Correlation between siblings strongly suggests that a genetic factor is involved in determining the height of the arch in children.

The authors wish to acknowledge the cooperation of the members of the Physical Growth Department of the Fels Research Institute, and especially the work of Janet Lipford and Jean Inman on statistical computation.

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THE SIGNIFICANCE OF THE WIDAL REACTION IN ENTERIC DISEASES OF CHILDREN

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THE diagnosis of typhoid fever is usually made on the basis of clinical symptoms and signs corroborated by laboratory findings. Since the symptoms are not as a rule pathognomonic, the clinician usually relies on the laboratory findings for his final decision on the diagnosis. Leucopenia is considered confirmatory evidence. A Widal test and blood and stool cultures usually decide the diagnosis. Since the Widal test can be performed quickly in any laboratory, while blood and stool cultures are more extensive and time-consuming procedures and require better laboratory facilities, it is not unusual, particularly if the patient is at home, for the doctor to rely on the former rather than on the latter procedure for his diagnosis. This is particularly true of physicians who treat children. It is uncommon to obtain positive Widal tests in normal children even in titers of 1:40 or 1:80, while normal adults frequently have agglutinins against typhoid in their blood in these dilutions. The physician, therefore, feels that in the presence of suspicious symptoms and a leucopenia, a positive Widal test is definite proof that he is dealing with a case of typhoid fever. This is not true, however. Positive Widal tests are obtainable in children as well as in adults, even in high dilutions, when there has been an infection with an organism of the Salmonella groups. The following case reports will exemplify this:

CASE 1.—M. P., female, became ill on Sept. 28, 1942, with chills, fever, vomiting, diarrhea, and abdominal cramps. Symptoms continued, and on October 3 she was hospitalized. The gastrointestinal symptoms subsided, but fever continued, although at a lower level. Typhoid fever was suspected, and blood for a Widal test was taken on October 7. It was positive in a dilution of 1:1280 in the O antigen of typhoid and 1:80 in the H antigen. A diagnosis of typhoid fever was made. The fever reached normal on October 13 and remained normal thereafter. Specimens of the patient's stools were requested. These were reported by the enteric fever laboratory of the New York City Department of Health as positive for *Salmonella eastbourne*. No typhoid bacilli were found.

CASE 2.—A. R., male, 6 years of age, became ill on June 16, 1942, with abdominal cramps, diarrhea, vomiting, and fever of 102° F. Abdominal symptoms abated after two days, but fever continued and did not reach normal for ten days. A Widal test was done on June 26 and showed agglutination in a dilution of 1:320 in the H antigen of typhoid and 1:160 in the O antigen. Typhoid fever was diagnosed. A stool specimen, submitted the same day, was reported by the enteric fever laboratory of the Department of Health as positive for *Salmonella enteritidis*. No typhoid bacilli were found.

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In order to clarify the meaning of the serologic reactions, a brief review of the classification of Salmonella is necessary. Salmonella is a large genus of serologically related, gram-negative, nonsporing bacilli, with motile flagella. These organisms ferment glucose, usually with but occasionally without gas production, but do not ferment lactose or sucrose. They are pathogenic for man and animals, or both.[1] Salmonella includes, therefore, the organisms commonly associated with food poisoning as well as the typhoid, paratyphoid A, and paratyphoid B bacilli. The only pathogenic organisms commonly associated with the enteric tract not covered by this definition are the bacillary dysentery group. Some members of the Salmonella group are pathogenic for animals only and not for man, such as *S. pullorum;* others are pathogenic for man and not for animals, such as *S. typhi* (*Bacillus typhosus*), *S. paratyphi* A (*B. paratyphosus* A), and *S. paratyphi* B (*B. paratyphosus* B). The majority are pathogenic for both, and the ones most commonly met with clinically are *S. cholerae suis* (hog cholera bacillus), *S. typhi murium* (*Bacillus aertrycke*), and *S. enteritidis* (Gärtner's bacillus). The classification of Salmonella was, for many years, in a chaotic state. Due to the efforts of several investigators, order has been achieved. The classification generally accepted today is the one recommended by the Salmonella Subcommittee of the Nomenclature Committee of the International Society for Microbiology and generally known as the Kauffmann-White Schema. A number of species has been added since the original report, but they are easily placed in the schema. The classification is on a serologic basis. In Table I is given a short outline of the schema, including only those organisms recovered more commonly in the laboratory of the New York City Department of Health in the past year. The complete table will be found in the Committee's report.[2]

It will be noted that Salmonella is divided into a number of groups and that each group is made up of many species. The groups are distinguished serologically by different O antigens, while the species are characterized, in addition, by different H antigens.

Most clinicians are aware that the typhoid bacillus has two antigens known as O and H. The O antigen is obtained from the body, or soma, of the bacillus and the H antigen, from the flagella. Since organisms in the Salmonella group are motile and have flagella, they all have O and H antigens. It is not generally known that the O and H antigens are not simple bodies, but that each is composed of a group of antigens. By proper laboratory procedures the separate antigens making up the groups O and H can be obtained. In the Kauffmann-White Schema the antigens making up the complex O are given Roman numerals and the antigens making up the H complex are given small letters as designations. Each species of Salmonella can, therefore, be given an antigenic formula. Thus, the typhoid bacillus (*S. typhi*) has the antigenic formula IX, d, while the paratyphoid A bacillus has the formula II, a. Classification of Salmonella is, therefore, a comparatively simple pro-

TABLE I

THE KAUFMANN-WHITE SCHEMA

TYPE	O ANTIGEN	H ANTIGEN	
		PHASE 1	PHASE 2
Group A			
S. paratyphi A	(I) II	a	–
Group B			
S. paratyphi B		b	1, 2
S. typhi murium	(I) IV V	i	1, 2
S. derby		f, g	–
Group C			
S. paratyphi C	VI, VII (Vi)	c	1, 5
S. choleraesuis		(c)	1, 5
S. oranienburg	VI, VII	m, t	–
S. montevideo		g, m, s	–
E. newport		e, h	1, 2
S. muenchen	VI, VIII	d	1, 2
Group D			
S. typhi	IX (Vi)	d	–
S. enteritidis	IX	g, m	–
S. panama	IX (I)	l, v	1, 5
S. eastbourne	IX	e, h	1, 5
Group E			
S. give		l, v	1, 7
S. anatum	III, X, XXVI	e, h	1, 6

The antigens in parentheses may fail.

cedure if the specific antisera are available. To group an unknown organism the slide agglutination technique is used. A drop each of antisera II, IV (VI, VII), (VI, VIII), IX, and (III, X, XXVI) is placed on a glass slide. To each of the six drops is added a drop of suspension of the unknown organism. If agglutination takes place with one of the drops, let us say IX, and not with the others, the organism belongs in Group D. To identify the member of the group, one goes through the slide agglutination technique again, using drops of antisera of the H antigens in the group. Thus, if it is found that the unknown organism, which we now know is in group D, agglutinates with antiserum d and not with the others, its formula is IX, d, and the organism is *S. typhi*. It is necessary to explain phase 2 of the H antigen. It has been found that colonies of young cultures of Salmonella have only the phase 1 antigen. However, in older cultures some of the colonies will have phase 1 antigen and others will have another antigen, the phase 2 antigen. The latter is nonspecific, and as can be seen from Table I, may appear in members of different groups. It is designated by Arabic numerals.

It now becomes obvious why a positive Widal test is not diagnostic of typhoid fever. In the patient in Case 1 the organism recovered from the stools was *S. eastbourne*. This is in group D and has the same O antigen as the typhoid bacillus. The individual's serum will, therefore, agglutinate the O antigen of typhoid. Similarly, in the patient in Case 2 the organism recovered was *S. enteritidis*, which, likewise, is in group D.

When the clinician makes a diagnosis of paratyphoid fever on the basis of suspicious clinical symptoms, a leucopenia, and agglutination

by the patient's serum of paratyphoid A or B organisms, he is on even more uncertain ground than in making a diagnosis of typhoid fever, since most laboratories do not report agglutinations with the O and H antigens of paratyphoid A and B as they do with typhoid. In the following report a diagnosis of paratyphoid B fever was made on the basis of a Widal test which was positive for paratyphoid B in a high dilution.

CASE 3.—A. M., male, 3 months of age, became ill on March 24, 1942, with an acute upper respiratory infection, colic, and fever. Three days later diarrhea developed. Previous to his illness he had been on a formula of evaporated milk, Karo syrup, and water and had been thriving. As his symptoms continued without improvement, he was hospitalized on March 28, and a specimen of his blood was sent to the hospital laboratory on March 30. The report of the Widal test was positive for paratyphoid B in a dilution of 1:1280. A diagnosis of paratyphoid B fever was made. A specimen of his stool was examined in the laboratory of the New York City Department of Health and was positive for *S. typhi murium*. The child made an uneventful recovery in a few days.

Reference to Table I will indicate that certain antigens occasionally appear in more than one group. Thus antigen I is occasionally found in Groups A, B, and D. It is obvious, therefore, that the serum of individuals infected with organisms in any of these groups may give cross agglutination reactions with organisms of the other groups. This is illustrated in the following report:

CASE 4.—E. S., female, 6 years of age, was hospitalized in 1940 because of fever and joint pains. She gave a history of joint and bone pains for the previous eight months. She had contractures of several joints and swelling of the legs and ulceration over the left ankle. A Widal test done on Feb. 6, 1941, showed agglutination in the O antigen of typhoid in a dilution of 1:40, in paratyphoid A in a dilution of 1:160, and in paratyphoid B in a dilution of 1:320. She developed abscesses over several joints, and the pus from these abscesses as well as stool specimens taken on different occasions from February to August were all positive for *S. typhi murium*.

COMMENT

It seems clear, from what has been said, that a positive Widal reaction cannot be considered clear proof of the diagnosis of typhoid or paratyphoid fever. It is of great help in the diagnosis, and gives presumptive evidence, particularly in children, that an infection with one of the Salmonella organisms has taken place. To make a definite diagnosis of typhoid fever, bacteriologic evidence is necessary. In the first week of the illness this is frequently obtained from blood cultures; in later weeks, from cultures of stool specimens. The latter can be obtained much more commonly than practicing physicians appreciate. During 1941 the laboratory of the New York City Department of Health reported positive stool cultures in 90 per cent of the patients with reported cases of typhoid fever. When it is realized that many of these cases were not reported until late in the disease, sometimes not before the fourth week, and that some of the cases may not have been typhoid

but were accepted as such on the basis of the physician's firm clinical conviction, it must be obvious that a positive culture can be obtained in almost all cases. It is, therefore, important for physicians to readjust their thinking and become accustomed to submit stool specimens, especially after the first week, at the same time that they submit blood specimens for a Widal test.

The question may be raised whether the discussion is not purely academic. What difference does it make whether the causative organism of the infection is typhoid or paratyphoid B or *S. typhi murium?* There are very important differences. Clinically, typhoid and paratyphoid fevers are more serious, are longer drawn out, and have higher mortalities than the fevers caused by the other Salmonella organisms. Epidemiologically, too, the differences are great. Carriers of typhoid and paratyphoid occur in from 5 to 10 per cent of all cases. They are chronic and a continuous danger to the community. They have to be kept under supervision by health departments and their movements and occupations restricted. On the other hand, infections with the so-called food poisoning Salmonella organisms are usually short lived, and chronic carriers of the organism are uncommon. Occasionally, individuals will carry the organism for weeks or months after the acute illness, but in most cases the carrier state soon ceases. They do not become a public health hazard.

CONCLUSIONS

1. The diagnosis of typhoid or paratyphoid fever on the basis of a positive Widal test is not justifiable. Such a positive test may be the result of an infection with another member of the Salmonella group.

2. The classification of Salmonella has been referred to, and illustrative examples have been given of positive Widal tests where the infecting organism is a member of the same or of a different group of Salmonella.

3. It has been stressed that the recovery of the typhoid or paratyphoid bacillus from the blood or stool is necessary for a definite diagnosis, and it has been pointed out that the organisms can be recovered in almost all cases.

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MENINGOCOCCEMIA

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INTRODUCTION

IT IS of interest that within the past year cases of meningococcemia without meningitis have been recorded.[1, 2, 3, 10] In one instance[10] a patient with meningococcemia without meningitis, although untreated, made a complete recovery. It was shown that bactericidal power developed in the blood of this patient to his own infecting strain of meningococcus. The following communication summarizes this case and reports two additional cases in patients with meningococcemia without meningitis. These patients were not treated with any chemotherapeutic agent or specific serum and all three recovered. Blood bactericidal studies are shown.

CASE REPORTS

CASE 1.—This case was reported in a publication[10] in 1941. The patient, L. B., was a male, aged 3 years, who was admitted in October, 1939, with meningococcemia caused by a type II meningococcus with a mouse-mucin virulence of 10^{-7}. He did not receive either sulfonamide or serum and made a complete recovery. Studies on the bactericidal effect of his blood from the third to the seventh day of hospitalization revealed that the patient's blood developed bactericidal power to his own strain of meningococcus. The cerebrospinal fluid was clear and sterile. The bactericidal findings are seen in Table I.

CASE 2.—The patient, R. A., male, aged 4 months, was admitted Jan. 15, 1942, with a temperature of 102.4° F., a complaint of irritability, and swelling of the right elbow for from one to four days. The family and past histories were irrelevant. On examination the baby was irritable but did not appear very ill. There were no meningeal signs. The spleen was palpable, and the area around the right elbow was swollen, tender, and inflamed. A diagnosis of septic arthritis of the elbow joint was made. Because the patient appeared only slightly ill no treatment with chemotherapeutic agents or serum was instituted. The baby improved rapidly during the first two days in the hospital, and his temperature was normal for most of the first week. Laboratory studies revealed the following findings: On January 16 and 17 the blood cultures were positive for meningococcus type II. On January 18 the blood culture was sterile. Bactericidal findings are seen in Table II.

CASE 3.—The patient, B. C., male, aged 5 years, was admitted Jan. 17, 1942, with a complaint of headache and vomiting four days before. Spots appeared over his trunk and extremities two days before admission, and he complained of soreness in his knees and in the back of his neck. The family and past histories were irrelevant. On examination the child did not appear very ill; in fact, he was

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sitting up in bed reading a book. There was a purpuric rash, mainly on the arms and legs, but some spots were seen on his back and buttocks. His left index finger, as well as both knee joints, was red, swollen, and tender. His temperature on admission was 101.2° F. but rapidly became normal, and he had no fever for the greater part of his first week in hospital. He made a complete recovery without the use of sulfonamides or serum. Laboratory studies revealed the following findings. On January 11 smears of the purpuric lesion showed the presence of gram-negative diplococci. A blood culture taken January 17 was positive for meningococcus type I, and the blood culture of January 18 was sterile. The cerebrospinal fluid was clear and sterile. Bactericidal studies were done on this patient's blood and they revealed the findings seen in Table III.

TABLE I

BACTERICIDAL EFFECT OF PATIENT'S (L. B.) BLOOD ON HIS STRAIN OF MENINGOCOCCUS

BLOOD	CULTURE DILUTION					BLOOD CULTURE
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	
First hospital day	No blood examined					+
Second hospital day	No blood examined					
Third hospital day	+	+	–	–	–	
Fourth hospital day	+	–	–	–	–	
Fifth hospital day	–	–	–	–	–	
Sixth hospital day	–	–	–	–	–	
Seventh hospital day	–	–	–	–	–	

+ = Confluent growth.
– = No growth.

TABLE II

BACTERICIDAL EFFECT OF PATIENT'S (R. A.) BLOOD ON HIS STRAIN OF MENINGOCOCCUS

BLOOD	CULTURE DILUTION					BLOOD CULTURE
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	
First hospital day	No blood examined					
Second hospital day	No blood examined					+
Third hospital day	No blood examined					+
Fourth hospital day	No blood examined					–
Fifth hospital day	+	+	+	+	+	
Sixth hospital day	+	–	–	–	–	
Seventh hospital day	–	–	–	–	–	

+ = Confluent growth.
– = No growth.

TABLE III

BACTERICIDAL EFFECT OF PATIENT'S (B. C.) BLOOD ON HIS STRAIN OF MENINGOCOCCUS

BLOOD	CULTURE DILUTION					BLOOD CULTURE
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	
First hospital day	No blood examined					+
Second hospital day	No blood examined					–
Third hospital day	No blood examined					
Fourth hospital day	–	–	–	–	–	
Fifth hospital day	42	13	–	–	–	
Tenth hospital day	–	–	–	–	–	

+ = Confluent growth.
– = No growth.
Figure = number of colonies.

DISCUSSION

In a number of previous communications evidence has been presented of the possible association of the bactericidal power of blood with

immunity to and recovery from meningococcal infection. Silverthorne and Fraser[4] demonstrated the development of bactericidal power in the blood of two infants with meningococcal meningitis who had been treated with antimeningococcic serum. In another instance bactericidal power was found in the blood of a child who had had meningitis four years previously. Certain studies[5-10] have shown that animals and human beings injected with meningococcus vaccines develop bactericidal power in their blood; additional findings suggested that the bactericidal power of blood is related to immunity to meningococcal infection. The three cases reported in this publication furnish evidence, first, that certain patients with meningococcemia do recover without drug or serum treatment and, second, that bactericidal power develops in their blood. Previous observations and the results obtained in patients in the cases reported show that other factors are responsible for the recovery of patients with meningococcal infection in addition to the type of treatment used. It should be pointed out that such factors must be considered in the compilation of case fatality rates based on results obtained with different forms of treatment.

SUMMARY

In the three cases of meningococcemia reported, none of the children received any chemotherapeutic agent or serum and each recovered. Bactericidal power developed in the blood of each patient to his infecting strain of meningococcus during the course of his illness. In two patients the strain was type II and in one patient, type I.

Clinical evidence is presented which supports the contention that other factors than the type of therapy used are responsible for recovery from meningococcal infection.

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POSTRUBELLA ENCEPHALOMYELITIS

Report of Cases in Detroit and Review of Literature

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GERMAN measles is generally considered a benign disease with few complications. In recent years, however, reports of several cases of encephalomyelitis complicating rubella have appeared.

This paper reports fourteen new cases of post-German measles encephalomyelitis and summarizes the clinical features of thirty-four cases previously reported. The outstanding features of the previously reported cases and those now first reported are included in Table I.

During the first six months of 1942 over 9,000 cases of German measles were reported in Detroit. It is likely that only one in ten cases of rubella is actually reported. Applying this ratio, it is estimated that there were 75,000 cases in the Detroit area during this period, resulting in one case of postrubella encephalomyelitis for 6,000 cases of rubella. The epidemic reached its peak in March, at a time when approximately one-half of the cases of German measles had been reported and eight of the fourteen encephalomyelitis cases had developed.

Signs and Symptoms Encountered in Patients in Fourteen Detroit Cases.—Because of the widespread involvement of the central nervous system, marked variations in signs and symptoms occurred. The earliest and most frequent complaints were headache (eight patients) and vomiting (seven patients). Stiffness and pain in the neck and extremities were common symptoms (ten patients). Severe, persistent convulsions and coma marked the four fatal cases and were present in eight of the total number of patients. Less frequently noted was inequality of pupils; absent, unequal or exaggerated deep reflexes; defects in speech; muscular twitching; and respiratory depression.

Type of Encephalomyelitic Course.—The course of postrubella encephalomyelitis is characteristically short. Whether mild or severe, the duration of the illness is brief. Mild cases presented only such complaints as headache, vomiting, and stiff neck; the illness rapidly subsided. Fatal cases were remarkable for their severe, persistent convulsions, and for respiratory distress which was manifested by Cheyne-Stokes breathing or a slow respiratory rate and severe cyanosis. Death occurred in the four patients within three days of onset of the complication. In all others, except one, rapid recovery occurred in spite of the severity of encephalitic manifestations.

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Time of Onset of Encephalomyelitic Signs and Symptoms.—The first encephalomyelitic signs and symptoms appeared with striking consistency four days after the onset of the rash. However, variations within the limits of one to six days occurred. In most patients the rash had disappeared at the time of onset of encephalomyelitis, but in three patients the occurrence of an exanthem did coincide with central nervous system symptoms.

In all patients, including those whose cases were reported by others, an average interval of 3.9 days occurred between the onset of the rash and the first signs of encephalitis.

Sequelae.—Only one case with encephalomyelitic sequelae following rubella has been previously reported. Davison and Friedfeld[15] reported a case in a 7-year-old boy with ataxia of all extremities, tremor of the right hand, and a partial facial paralysis who improved gradually to recover completely within two months.

Case 1 (F. S.) in our series is striking for its prolonged sequelae. This patient developed ataxia, staccato speech, and propulsive gait during her acute illness. There has been gradual improvement, but after four months these signs have not entirely subsided.

Prognosis.—There were four deaths in our fourteen cases, and of the thirty-four cases previously reported, six deaths were recorded, giving a combined fatality rate of 20.8. The fatal cases ran their course rapidly; none of the patients survived more than three days after the onset of encephalitis. The patients who recovered improved rapidly and completely, except the one with persistent sequelae. All surviving patients have been re-examined at least once.

Diagnosis.—There is nothing diagnostic about the neurologic features of postrubella encephalomyelitis. Stiff neck, convulsions, vomiting, headache, and other neural complaints may well be part of any acute disease of the central nervous system. A history of German measles within a week prior to the onset of central nervous system signs, the presence of a fading maculopapular rash, or postauricular lymph nodes are all most helpful clues. The leucopenia of rubella becomes a leucocytosis with the onset of encephalitis.

Cerebrospinal Fluid.—Spinal fluid pressures ranged between 120 and 180 mm. of water in four patients. No readings were taken in the four patients with fatal cases. The spinal fluid sugar determination varied between 67 and 100 mg. per 100 ml. The protein was moderately increased, averaging 67.5 mg. per 100 ml. Cell counts varied from 8 to 500 cells (average, 91). Mononucleated cells predominated.

A Typical Case.—The clinical course of all patients is similar enough in general features so that the following case may be considered typical:

The chief complaint of a 10-year-old male was headache and vomiting of six hours' duration. It was noted that the patient was disoriented and his speech thick. At the end of six hours he suddenly fell to the ground with his eyes rolling and had a generalized convulsion. Physical

TABLE I

THE ESSENTIAL CLINICAL FEATURES OF FORTY-EIGHT CASES OF POST-GERMAN MEASLES ENCEPHALOMYELITIS

	AGE (YR.)	SEX	DAYS FROM ONSET RASH TO FIRST C.N.S. SIGN	FIRST C.N.S. SIGN OR SYMPTOM	OTHER C.N.S. SIGNS AND SYMPTOMS	SEQUELAE	DURATION OF C.N.S. SIGNS AND SYMPTOMS	MAX. TEMP. (°F.)
Cases Previously Reported								
Benard[1]*			6 (Average of 7 cases)		Variable encephalitic signs	None 1 death		
Brock[2]	23	F	3	Shooting pain; headache	Stiff neck; diplopia; retention	None	15 days	101.8
Debre[3]*	7	M	2					
Debre[3]	8	M	2					
Potter[4]	5	F	4	Vomiting; coma	Drooling; twitching	None	2 days (approx.)	
Gennes[5]			5					
Siegl[6]	9½	F	5	Headache	Spasm, unconscious; twitching	None	4 to 6 days	101
Skinner[7]	10	M	4	Irritability; unconsciousness	Confusion; headache	None		103
Briggs[8]†	10	M	3	Aphasia; convulsion	Babinski; Chaddock; Oppenheim; nystagmus	Expired Jan. 28, 1935		

*Original papers not reviewed.
†Autopsy.
‡No autopsy.
§Case of Dr. Robert J. Schneck, The Harper Hospital, Detroit, Mich.

The pathologic findings in these cases were obtained from Gabriel Steiner, Wolfgang W. Zuelzer, and William L. Brosius, whose help we gratefully acknowledge.

Briggs[8]	3	M	3	Semiconscious	Drowsy; spastic	None		
Merritt and Koskoff[9]	5	M	3	Convulsions	Right sided paralysis; semiconscious	None	7 to 9 days	100
Merritt and Koskoff[9]	33	F	3	Headache; dizziness; vomiting	Slurred speech; muscle incoordination	None	8 to 10 days	
Merritt and Koskoff[9]	14	M	6	Headache	Coma, twitching	None	9 to 12 days	
Merritt and Koskoff[9]	9	F	4	Suddenly unconscious	Confused; rigid; cyanotic; maniacal; no ankle jerk, knee jerk, or abdominal reflexes	None	9 to 10 days	105
Baumgartner[10]	10	F	4	Convulsion	Twitching			
Goldbloom and Keith[11]	14	F	3	Vomiting; convulsion	Coma; rigidity; drowsiness			
Barraclough[12]	12	M	3	Headache; dizziness	Convulsions; coma; memory defect three weeks	None	10 to 15 days	102.4
Barraclough[12]	7	M	4	Confusion; muscle twitching; headache		None	4 days	99.6
Read[13]	26	M	4	Thick speech; dizziness	Projectile vomiting; diplopia; nystagmus; stiff neck; headache	Fatigability 1 year; no objective sequelae	10 days	
Taylor[14]†	18	F	3	Pain in back, wrists, and ankles	Twitching; drowsy	Expired		
Davison and Friedfeld[15]†	22	M	5	Restless	Moaning; heavy head; stiff neck; Kernig; convulsion	Expired June 1, 1935	3 days	108 (Terminal)

TABLE I—CONT'D

	AGE (YR.)	SEX	DAYS FROM ONSET RASH TO FIRST C.N.S. SIGN	FIRST C.N.S. SIGN OR SYMPTOM	OTHER C.N.S. SIGNS AND SYMPTOMS	SEQUELAE	DURATION OF C. N. S. SIGNS AND SYMPTOMS	MAX. TEMP. (°F.)
Davison and Friedfeld[15]‡	23	F	3	Neck pain	Respiratory failure; vomiting; headache; stiff neck; bulbar palsies; cyanosis	Expired May 17, 1935	7 days	
Davison and Friedfeld[15]	13	F	3	Vomiting	Fierce scratching; disoriented	None	8 days	
Davison and Friedfeld[15]	7	M	Few days	Apathy	Tremor, ataxia (2 mo. ?)	None	60 days (Gradual improvement)	
Davison and Friedfeld[15]	8	F	Few days	Tetanic muscle spasms	Babinski and Brudzinski	Expired	1 day (approx.)	104
Davison and Friedfeld[15]	19	M	5	Headache	Projectile vomiting; drowsiness	None		
Welsh[16]	24	F	4	Headache	Dizziness	None	?	99.4
Owen and Greenway[17]	26	M	2	Headache	Back pain; retention	None	16 days	99.6
Author's Cases								
Case 1 (F. S.)	3½	F	5	Vomiting	General convulsions; stiffening spells; stiff neck; Kernig and Babinski; coma	Ataxia; aphasia	120 days +	103.2
Case 2 (H. M.)	9½	M	4	Dim vision	General convulsions; coma	None	3 days	102.2
Case 3 (S. S.)	5⅓	F	4	Headache; vomiting	Neck pain	None	3 days	101

Case 4	(R. C.)†	6	M	6	Drowsy; vomiting	Delirium; coma; convulsions; slow respiration	Expired March 21, 1942	3 days	
Case 5	(B. E.)	11	F	5	Headache; stiff neck	Kernig; unequal tendon reflexes	None	3 days	100.2
Case 6	(H. B.)	14	F	4	Vomiting; severe convulsion	Kernig; Brudzinski; coma five days; leg pain	None	8 days	105.5
Case 7	(J. S.)	6	M	1	Headache; convulsion; vomiting	Thick speech	None	10 days	104
Case 8	(T. F.)	9	M	5	Headache; vomiting; coma	Kernig; right Babinski; stiff neck and back; disoriented	None	3 days	102
Case 9	(M. M.)†	5	F	3	Convulsion persistent 6 hours (to death)	Cyanosis	Expired	¼ day (6 hr.)	105.6
Case 10	(J. G.)†	10	F	4	Headache; convulsion; stiffening	Absent abdominal reflexes; rigidity; Cheyne-Stokes resp.	Expired May 16, 1942	2 days	106.5
Case 11	(S. H.)§	16	F	3	Stupor (semicoma)	Sluggish pupils; unequal tendon reflexes; response to painful stimuli only	None	3 days	102
Case 12	(B. F.)	11	F	3	Stiff and painful neck	Painful right leg	None		100.2
Case 13	(J. F.)‡	6	F	3	Headache; lethargy	Persistent convulsions; Cheyne-Stokes resp.; coma; stiff neck, and back	Expired July 8, 1942	3 days	107 108
Case 14	(G. S.)	24	M	1	Headache; stiff neck	Irrational and restless; diplopia; left facial weakness	None	3 days	101

examination revealed a few faded macular spots on the buttocks, some enlarged postauricular glands, and positive Kernig and Babinski signs. Respirations were of the Cheyne-Stokes type and the color was cyanotic. At irregular intervals the extremities became spastic and tremulous. Additional history indicated that a generalized rash had been present for the past three days and that the patient had had no fever and had been up and about during this time. At the time of the seizure the temperature was 103° F. Examination of the spinal fluid revealed eighty mononucleated cells, a plus 1 Pandy test, 80 mg. per 100 ml. of sugar, and a spinal fluid pressure of 180 mm. of water.

The boy remained in a stuporous state for thirty-six hours, during which time he had several convulsive spells. He then began to breathe more easily and, as his fever subsided, he gradually regained consciousness. No abnormal neurologic signs were present five days after the onset of the convulsions. Recovery was complete.

Pathology.—Three of the four patients with fatal cases were examined.

Gross Examination: There was marked brain swelling in two patients with associated flattening of cerebral convolutions, narrowing of sulci, and a cerebellar pressure cone. In the remaining patient there was generalized capillary hyperemia of the white matter of the cerebral hemispheres.

Microscopic Examination: Numerous sections from various parts of the brain were available in each case. Perivascular infiltrating cells in two patients were mononuclear cells of plasma cell-like character. In one patient yellowish pigment was seen occasionally in the Virchow-Robin spaces along with lymphocytes and monocytes. No demyelinization was noted around vessels as is frequently noted in measles and postvaccinal encephalomyelitis. Nerve cell damage was observed in two patients, but no specific nerve cell lesions were seen. Small capillary hemorrhages were particularly marked in the floor of the fourth ventricle in two patients. The pathologic changes were limited to the mesencephalon and part of the diencephalon in two patients and to the white matter of the cerebrum and the corpus striatum in the remaining one.

Only three necropsy reports are published in the literature. In 1935 Briggs[8] described perivascular infiltration with polymorphonuclear leucocytes and lymphocytes, scattered petechial hemorrhages both grossly and microscopically, and slight flattening of the convolutions grossly. In 1937 Taylor[14] reported a postrubella death with pathologic findings comparable to ours. The most complete study was made by Davison and Friedfeld[15] in 1938. The findings in this report are similar to ours, except for the mild meningitis and the generally more extensive involvement.

SUMMARY

Fourteen new cases of encephalitis following German measles are reported and the clinical features of thirty-four previously reported cases summarized.

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EFFECTS OF POLIOMYELITIS VIRUS ON THE URINARY BLADDER OF RABBITS

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SOME years ago, attention was drawn to the fact that many poliomyelitis patients have paralysis of the urinary bladder and that this occurs even though there is no paralysis of muscles which derive their nerve supply from the same segments as the bladder.[1] It was also pointed out that this organ is often involved long before somatic paralysis appears in peripheral muscles. From these facts, it could be reasoned that the paralysis is not central in origin or due to any lesion in the cord. It might, however, be peripheral in character; that is the end fibers of the detrusor nerves in the bladder might be involved. Were this true, the virus would have to be present in the urine.

It is fully appreciated that the bladder is not an adsorptive organ. Yet, if virus were excreted through the kidney and collected in the urinary bladder before excretion and the organ dilated at any time, the virus, which has nearly an obligate affinity for gray fibers, might approximate the gray fibers of the detrusor and branches of the ileohypogastric nerves and cause the condition that appears clinically; that is, paralysis of the bladder with overflow dribbling.

Previously it had been shown that there is an enterodepressant factor in the stools and spinal cords of monkeys afflicted with poliomyelitis which depressed the intestines of rabbits.[2] The intestinal strips obtained from these animals were so sensitive to the poliomyelitis factor that this animal was selected for our subsequent experiments on the bladder. The objective was to fill the bladder of the rabbit with various suspensions of virus and other materials and to note the results.

In the first experiment (1934), twenty-two male rabbits were used. Experiments done on two female animals were discarded because it was technically difficult to keep the catheter in place. In each experiment the animal was anesthetized with sodium phenobarbital, 0.35 Gm. per kilogram subcutaneously. The lower abdomen was shaved, an incision made along the midline, and the bladder exposed. Warm mineral oil was kept in the abdominal cavity to avoid the effect of air currents. The animal was tied to a board and an infant's catheter passed through the penis into the bladder. String was then tied several times around the penis to prevent leaks and to keep the catheter in place. The catheter

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was connected with a water manometer, the oscillations of which were recorded on a revolving smoked drum. The contractions of the bladder were studied visually and recorded mechanically after various stimuli, such as slapping the abdomen, the bladder, etc. The test substances were saline, "enteric toxin,"[2] 10 per cent poliomyelitis virus suspension, and a combination of 10 per cent virus and enteric toxin suspension.

The response was erratic. There was no directive tendency. When the bladder was dilated with the virus-enteric toxin mixture and kept dilated by sustaining pressure on the catheter for a few minutes so that possible approximation could occur, the organ became permanently affected and atonic so that it would not subsequently respond to stimuli. This, however, meant little or nothing when it was found that the same dilatation and the same results were obtained in control animals merely dilated with saline, although the atony seemed to be more slowly produced in the latter instance.

The fact that the abdomen had been opened created an artificial condition. There also may have been too much resistance in the mechanical setup, which prevented a record being made of the finer contractions of the bladder. For these reasons, we decided to repeat the experiments several years later (1939).

Eighteen male rabbits were used. They were anesthetized in the same manner as previously, but the abdomen was not opened. This time the catheter was connected with a Trattner hydrophoragraph, an instrument sensitive enough to pick up oscillations caused by a single drop of urine and to register the reaction on a revolving drum.[3] All the test materials mentioned previously were tried again, but without success.

Thus, we failed to demonstrate that poliomyelitis virus or any combination of virus and enteric toxin could cause paralysis of the rabbit bladder when injected therein.

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ATTEMPTS TO RECOVER POLIOMYELITIS VIRUS FROM FRUIT, WELL WATER, CHICKEN CORDS, AND DOG STOOLS

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EPIDEMICS of poliomyelitis usually coincide with the harvesting seasons of perishable fruits both in the north and south temperate zones.[1] The virus can be found in the gastrointestinal tracts of patients with this disease.[2] Histories of dietary indiscretions previous to an attack are not uncommon. These three facts led us to suspect that the virus might be found in or on unwashed fruit, in well water, in the stools of sick animals, and in the cords of chickens sick with paralysis. All of these factors were often found in the neighborhood where poliomyelitis patients lived.

As a preliminary to the present study, we examined the washings from some fruits. Every year for eight years, grapes, apples, peaches, and pears were collected from the vineyards and trees in northern Ohio at the time of ripening. The fruit was cut away from the tree or vine with sterile scissors and handled in sterile towels. On return to the laboratory, it was washed in sterile physiologic saline and the washings cultured on hemoglobin blood agar. Despite the so-called virucidal power of the sun, we have always been able to isolate from these washings nearly every organism usually found in the human gastrointestinal tract. From one specimen (1937), a streptococcus was isolated. Whether these organisms play any part in the production of poliomyelitis is unknown. It could be concluded, however, that any fruit should be washed before eating.

In the present experiments, an attempt was made to isolate the virus of poliomyelitis from the following specimens.

1. About a peck of fruit was washed over and over again in 3,000 c.c. of sterile distilled water. The washings were placed in the largest type of sausage casing purchasable* and hung from supports. An electric fan was turned on the casing until the contents were concentrated to 120 c.c. The latter was filtered through Mandler N and W filters. This was termed "washings concentrate."

2. About two quarts of peelings from fruits (apples, peaches, pears, plums, etc.) were ground in a Waring blender while sterile distilled cold water was slowly added, the amount of water used depending upon the amount of fruit being processed at the moment. This mass was

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Sponsored by a grant from The National Foundation for Infantile Paralysis, Inc.
*Visking.

TABLE I

PROTOCOL OF RESULTS FROM VARIOUS TESTS

MATERIALS	PATIENT	MONKEY	PLACE OF INJECTION				RESULTS
			INTRACEREBRAL	INTRANASAL	SUBCUTANEOUS	INTRAPERITONEAL	
W.C.	1	1	1 c.c. Aug. 26, 28	1 c.c. Aug. 26 to Sept. 18		40 c.c. Aug. 26; 30 c.c. Sept. 3, 5, 8, 12, 16, 18	Negative
W.C.	2	2	1 c.c. Aug 26	1 c.c. Aug. 26 to Sept. 6		40 c.c. Aug. 23-28, Sept. 2, 4	Negative
W.C.	3	3	1 c.c. Aug. 26, 28	0.5 c.c. Aug. 26; 1.0 c.c. Aug. 27 to Sept. 18		40 c.c. Aug. 26, 29, Sept. 3, 5, 8, 11, 12, 16, 18	Negative
W.C.	4	5	1 c.c. Aug. 21, 23	1 c.c. Aug. 23 to Sept. 6		40 c.c. Aug. 18, 20, Sept. 2, 6	Negative
W.C.	5	5	1 c.c. Aug. 22, 23	1 c.c. Aug. 18 to 28		40 c.c. Aug. 18, 20, 23, 25	Negative
F.C.	5	5		1 c.c. Aug. 29 to Sept. 6		40 c.c. Aug. 29, Sept. 2, 4, 6	Negative
W.C.	6	6		1 c.c. Oct. 3, 6, 7, 11, 13	10 c.c. Oct. 11, 30; Nov. 11	Oct. 3, 20 c.c.; 40 c.c. Oct. 11, 13; 5 c.c. Oct. 14	Furred Oct. 9 and Oct. 10

W.C., Washings concentrate; F.C., fruit concentrate; D.W.C., Duponol washings concentrate; D.F.C., Duponol fruit concentrate; W.W.C., well water concentrate; D.Wa.C., Duponol water concentrate; D. W. W., Duponol well water; W.W.C., well water concentrate; D.S.C., dog stool concentrate; C.C.S., chicken cord suspension (10 per cent).

*One died ten minutes postinjection.

†The result in two animals was negative; 1 died six weeks and one, a day after the injection. There was no evidence of poliomyelitis. One animal had weakness of the legs but no paralysis and died on the sixth postinjection day. Post-mortem examination was negative. A suspension of the cord transferred to another monkey gave negative results.

‡All died from seven to ten days postinjection. Cord and brain transfer experiments were negative after four generations of injections.

TABLE I—CONT'D

MATERIALS	PATIENT	MONKEY	PLACE OF INJECTION				RESULTS
			INTRACEREBRAL	INTRANASAL	SUBCUTANEOUS	INTRAPERITONEAL	
F.C.	6	6		1 c.c. Oct. 15, 20	10 c.c. Oct. 15, 20	40 c.c. Oct. 15 and 20	Negative
W.C.	7	7 and 8				40 c.c. Oct. 3, 12	Negative
D.W.C.	7	9 and 10		1 c.c. Oct. 13	10 c.c. Oct. 13	40 c.c. Oct. 13	Negative
W.C.	8	11		1 c.c. Oct. 13	10 c.c. Oct. 13	20 c.c. Oct. 13	Negative
D.F.C.	9	12	1 c.c. Oct. 10, 13	1 c.c. Oct. 7, 10, 13	10 c.c. Oct. 7, 10, 13	30 c.c. Oct. 7, 10, 13	Negative
F.C.	10	13		1 c.c. Oct. 15, 20	10 c.c. Oct. 15	40 c.c. Oct. 15	Oct. 25, clumsy; no polio
W.W.C.	4 sources	14 and 15 16 and 17	1 c.c.	1 c.c.	10 c.c.	40 c.c. daily for 4 days	Ill; no polio
D.Wa.C.		18 and 19 20 and 21	1 c.c.	1 c.c.	10 c.c.	40 c.c. daily for 4 days	Negative
W.W.C.		22 and 23				100 c.c.	Negative*
D.W.W.		24		0.5 c.c. daily for 30 days		30 c.c. daily for 20 days	Negative
W.W.C.		25 and 26				40 c.c. daily for 15 days	Negative
D.S.C.		27 and 28 and 29 30 and 31	1 c.c.	0.5 c.c. daily for 6 days	10 c.c. 10 per cent	40 c.c.	Negative†
C.C.S., 10 per cent		Eastern cotton rats	0.05 c.c. twice 5 days apart	0.06 c.c. daily for 7 days	0.5 c.c. daily for 3 days	1.0 c.c. daily for 3 days	No polio‡

concentrated in the same manner as were the washings and was termed "fruit concentrate."

3. Specimens of well water obtained from scattered sources were concentrated as were the fruit specimens.

4. Specimens of fruit and well water were also prepared by treating them with Duponol in the usual manner.[3]

5. Cords from chickens sick with paralytic disease were prepared in 10 per cent suspension in the usual way by grinding the sample in normal physiologic saline.

6. A small epidemic occurred in Akron, Ohio.[4] Dr. Carl E. Krill of Akron Children's Hospital found that two dogs had died in the same neighborhood. One animal had been buried, but the second one was obtained. Two other dogs living nearby had been ill at the same time. Stools were obtained from the animals and prepared in the usual manner.[2]

The above specimens, "fruit washings," "fruit concentrate," and "well water," were not only injected into monkeys, but also into eastern cotton rats with negative results. (Description of rat injections do not appear in Table I.) Chicken cord suspensions killed the rats and we were able to transmit some lethal factor for three doses, after which the results of reinjections were negative.

The amount of injection of each specimen, the material injected, and the results are noted in Table I.

CONCLUSION

Attempts were made to recover poliomyelitis virus from fruit (washings), well water, stools from sick dogs, and cords from paralyzed chickens found in vicinities where human poliomyelitis had occurred. Although the virus may have been present in the specimens tested, its existence could not be demonstrated when either the eastern cotton rat or the *Macaca mulatta* monkey was used as the test animal.

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ATTEMPTS TO ISOLATE POLIOMYELITIS VIRUS FROM URINE

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BLADDER paralysis is commonly found in poliomyelitis. This paralysis is not central or cord in character.[1] It might be peripheral, however. If it were, it would be the result of local approximation of virus and the end fibers of the nerves supplying the detrusor of the bladder and internal sphincter of the penis; therefore, the virus would have to be present in the urine.

Sabin and Ward[2] tried to isolate virus from the urine of human beings, but their results were negative. They used large quantities of urine (up to 200 c.c.) obtained from twelve patients, six of whom had bladder paralysis.

Kessel and co-workers[3] obtained questionable results in one instance, the monkey developing weakness nine days after having been injected with urine. Unfortunately, this animal had previously been inoculated intranasally with a suspension of human poliomyelitis stool. Although the animal remained asymptomatic for six weeks, it is still possible that it might have been in the incubation period when subsequently inoculated with urine. From a pathologic standpoint, this animal's cord was suggestively positive, but it was not infective when attempts were made to transfer it.

Not all patients develop bladder paralysis. In those who do, the condition may appear long after the agent causing it has disappeared from the urine. Bladder paralysis may appear early in the disease, often before somatic paralysis. Were virus in the urine, the question would be when to look for it.

It was thought that the virus would be found previous to, simultaneous with, or soon after the appearance of bladder paralysis. Since the disease is usually not diagnosed in the preparalytic stage, urine specimens could not be obtained from those patients in whom bladder paralysis appeared prior to somatic paralysis. Therefore, a concentrated study was made of those patients in whom bladder and somatic paralyses appeared somewhat simultaneously. The 1941 epidemic afforded a good opportunity to collect specimens from such patients, but only ten were seen who met our specifications.

A portion of every specimen of urine obtained immediately following the onset of bladder paralysis and for two days thereafter was col-

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lected and concentrated in the same manner as was the fly extract recently described.[4] In all, 5,000 c.c. of urine (representing over 125 individual urine specimens) were concentrated.

It was not known what kind of reaction a monkey would have after an intracerebral injection of urine concentrate; nonspecific reactions were expected, but only one abscess developed. Ten *M. mulatta* monkeys were given urine concentrate: 1 c.c. intracerebrally, 5 c.c. intraperitoneally, 5 c.c. subcutaneously and 1 c.c. intranasally. The subcutaneous and intranasal injections were continued daily for ten days; the intraperitoneal injections were repeated thrice, and the intracerebral injections once within twenty days. The subcutaneous injections were always followed by local edema and induration, and the intraperitoneal injections, by loss of appetite.

No animal showed any signs of the disease.

Thus the attempt to demonstrate the specific virus of poliomyelitis in the urine of patients with bladder paralysis was a failure when the monkey was used as the test animal, even though such specimens were obtained at an optimal time; that is, coincident with the onset of the paralysis.

In the next experiment urine was obtained at autopsy from Patient D, was Duponol treated, and 1 c.c. injected intraperitoneally, 0.6 c.c. intranasally, and 0.5 c.c. subcutaneously daily into five cotton rats for twenty-three days. The result were negative. Lack of monkeys led us to try eastern cotton rats, despite the fact that negative findings would not constitute proof of absence of virus. It was thought that they might be acclimated by frequent doses.

Urine was obtained at autopsy from Patient G and concentrated according to the method of Trask, Vignec, and Paul.[5] One cubic centimeter was injected intraperitoneally and 1 c.c. subcutaneously into two cotton rats; 0.5 c.c. subcutaneously for ten consecutive days; then 2.0 c.c. intraperitoneally daily for fifteen consecutive days. Because virus might be present and yet the animals show no symptoms, they were sacrificed at the end of this time. The cords and brains were combined, and a 20 per cent suspension prepared in saline and injected into a second group of three rats. Five-tenths of a cubic centimeter was injected subcutaneously every third day for four successive doses, the last 2 being combined with 1 c.c. of enteric toxin. The results were negative.

Urine obtained at autopsy from Patient B was mixed with equal volumes of enteric toxin. Five cubic centimeters were given intraperitoneally every third day to three cotton rats, following which one died on the tenth, one on the eleventh, and one on the sixteenth day; none showed paralysis. The spinal cords of these latter animals were combined and made into a 10 per cent suspension, which was prepared and injected into two other rats. The dosage was 0.6 c.c. intranasally, 0.6 c.c. intracerebrally, and 0.5 c.c. subcutaneously for four doses

every five to seven days. They remained normal and were sacrificed on the twenty-seventh day. A 10 per cent saline suspension of their combined spinal cords and brains was injected into two other rats in the usual way; that is, 0.06 c.c. intracerebrally, 0.06 c.c. intranasally, 0.5 c.c. subcutaneously, and 1.0 c.c. intraperitoneally. They received seventeen subsequent doses of 0.5 c.c. each subcutaneously. None of the animals showed any disease after three months.

Since the first group of rats injected in the last experiment had died, a collateral second group of two rats was injected with the same material in doses of 0.6 c.c. intranasally, 0.6 c.c. intracerebrally, 0.5 c.c. intraperitoneally with no results. Because the virus might have been in a latent state, the animals were killed on the seventh day, a 20 per cent saline suspension of their cords and brains prepared and injected into two rats—0.06 c.c. intranasally, 0.06 c.c. intracerebrally, 0.5 c.c. subcutaneously and 1.0 c.c. intracerebrally. They also received 0.5 c.c. subcutaneously for thirteen doses every third and fifth day. The results were negative. These animals were then sacrificed, their cords and brains combined, a 20 per cent suspension made and injected into five animals in the same manner as previously with no success. This experiment was discontinued five months later.

Thus the presence of the specific virus of poliomyelitis was not demonstrated in urine obtained post mortem from the bladders of poliomyelitis patients when the eastern cotton rat was used as the test animal.

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MEDIASTINAL EMPHYSEMA AND PNEUMOTHORAX FOLLOWING TRACHEOTOMY

Report of Four Cases

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IN THE hands of a competent surgeon, the procedure of tracheotomy is generally considered to be a minor operation and one not likely to have serious complications. However, such complications do rarely occur. The following cases are presented as instances of mediastinal emphysema and of pneumothorax as a result of tracheotomy and illustrate the grave nature of these occurrences.

Mediastinal emphysema and pneumothorax as complications of tracheotomy are not mentioned by some of the standard texts in diseases of the nose and throat. Figi,[1] in a review of 206 tracheotomies done at the Mayo Clinic, states definitely that there was no immediate surgical mortality attributable to the operation. However, many of these cases were adults, and comparatively few had marked respiratory distress. Jackson and Jackson[2] mention only mediastinal emphysema and state that it is especially apt to occur if the wound is sutured tightly around the cannula. Negus[3] states that acapnia may account for the distressing apnea which he has observed following introduction of the tracheal cannula. He did not consider the possibility of pneumothorax in his cases. Leiner[4] observed nine cases of mediastinal emphysema subsequent to tracheotomy prior to 1903; and pneumothorax following tracheotomy was noted by Iglauer[5] in 1915, Wiethe[6] in 1933, and Simpson[7] in 1937. Champneys[8] found autopsy records of 109 cases dying subsequent to tracheotomy in two London hospitals during the period 1860-1882. Eight of these cases showed mediastinal emphysema at autopsy; two cases exhibited the additional finding of pneumothorax. In one case the pneumothorax was bilateral and was stated to be the cause of death. Michels,[9] in 1939, described six cases, two of which resolved spontaneously; two were bilateral tension pneumothoraces and resulted fatally despite aspiration; and the other two were unilateral and resulted in one death. He also stated that pneumothorax recurred following aspiration in some of his patients and that closed drainage might become necessary. All of the reported cases (exclusive of Champneys' in which the age is not recorded) were those of *young children*, and, as is usual in this age group, the operation was in most instances done to relieve acute respiratory distress.

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CASE REPORTS

CASE 1.—A 2-year-old white male was admitted to the St. Louis City Isolation Hospital on Dec. 12, 1937, with a diagnosis of faucial and laryngeal diphtheria. This diagnosis was confirmed by culture. Some respiratory distress had been present during the preceding twenty-four hours, and at the time of the initial examination, he presented marked inspiratory stridor but only moderate suprasternal retraction. His color was good, and nothing abnormal was noted on examination of the lung fields. About twelve hours after admission, a direct laryngoscopic examination was made, followed shortly by tracheotomy under local anesthesia. Nothing abnormal was noted about the operation itself; the patient experienced immediate relief and within a few hours fell asleep. Constant nursing care assured, in so far as possible, a properly patent cannula at all times. Five hours postoperatively he gasped several times, the pulse became imperceptible, and respirations shortly ceased. The clinical impression was that death occurred as a result of diphtheritic cardiac failure.

An autopsy done five hours post mortem revealed *both lungs* to be collapsed closely against the mediastinum, which was in the midline and showed considerable emphysema. Both pleural domes were inadvertently removed in opening the thorax; however, no rupture could be demonstrated through the visceral pleural surfaces. There was no air noted in the subcutaneous or retroperitoneal tissues. The tracheobronchial tree was quite patent throughout. Microscopically the lungs showed areas in which the alveolar outlines were not recognizable, and there was considerable atelectasis. The myocardium was normal microscopically.

It is entirely possible, then, that this patient's death could have been due to the mediastinal emphysema and a bilateral tension pneumothorax and serves to emphasize the fact that tension pneumothorax may kill very quickly a patient who otherwise is progressing satisfactorily.

CASE 2.—A 14-month-old white male was admitted to St. Louis Children's Hospital on Dec. 20, 1941, with the diagnosis of a foreign body in the right main bronchus. The child had inhaled the foreign body some six hours prior to entry to the hospital and had exhibited spells of coughing and dyspnea and cyanosis since that time. Examination revealed the child to be crying vigorously but to have some dyspnea. The right lung field was emphysematous with the mediastinum shifted to the left. Immediate bronchoscopy was done and a grapefruit seed removed from the right main bronchus. Postoperatively the baby's color remained good, and he slept well that night. By morning his cry was hoarse, considerable retraction was noted, and the diaphragm moved but little when viewed in the fluoroscope. At this time the mediastinum was normal in position, and no emphysema was noted. A tracheotomy was then performed, respiratory relief followed, and the child was returned to the ward in good condition. Shortly afterwards (within twenty minutes) he was noted to be cyanotic and gasping for breath, and respiration quickly ceased. Immediate bronchoscopy revealed the main bronchi to be open and quite free of mucus and blood. Under the fluoroscope a bilateral pneumothorax was discovered, needles were inserted into the lateral aspects of each side of the thorax, and air immediately escaped under pressure.

At autopsy and prior to opening the thorax, air was introduced into each pleural cavity, but even though considerable pressure was used, no air bubbled forth from the tracheotomy wound. Thus, it was shown that air which somehow entered the pleural cavities prior to death could not be demonstrated to escape from them, and thereby considerable tension was produced. A moderate amount of atelectasis was noted in both lungs, but there was no air present in the mediastinal tissues. No tears were visible in the mediastinum or the visceral pleura.

Since this patient had been provided with an adequate airway and the bronchi were shown to be quite patent on direct vision, one cannot ascribe his death to causes other than the bilateral tension pneumothorax.

CASE 3.—A 12-month-old white male entered the St. Louis Children's Hospital on July 17, 1942. He had been in good health until the day of admission when he began to cough and to have respiratory difficulty and some cyanosis. Because of these symptoms, an emergency tracheotomy was done by the referring physician, a urinary catheter being used as an airway. On examination at this hospital the boy was mildly cyanotic and exhibited marked respiratory difficulty with considerable retraction of the intercostal spaces and the suprasternal notch. Low bronchoscopy was immediately performed, and a piece of bony gristle, presumably a chicken bone, was removed from the trachea a short distance above its bifurcation. Anteroposterior roentgenogram of the chest taken shortly after this procedure revealed normal lung fields.

On return to the ward, the patient's temperature was 41.4° C. and the respirations were very noisy, although not particularly labored. Treatment consisted of adequate parenteral fluids and chemotherapy. About four hours later the patient developed mild convulsive twitchings of the extremities, and soon afterwards the respirations became quite labored, together with long periods of apnea. Despite the administration of oxygen and additional parenteral fluids, his course continued rapidly downhill. He became comatose and exhibited marked tachypnea and retraction of the intercostal, subdiaphragmatic, and suprasternal regions. Fluoroscopy in the anteroposterior view showed increased bilateral hilar markings and questionable pneumothorax on the left, and in the lateral view a large collection of air was seen in the anterior mediastinum (Fig. 1). A needle was inserted into the anterior mediastinum, and although aspiration with an oiled syringe was attempted, no air was obtained. Another needle was inserted into the left pleural cavity low in the midaxillary line, but here, too, aspiration was unsuccessful.

Peripheral circulatory collapse, cyanosis, rigidity of the extremities, repeated convulsive episodes, and respiratory embarrassment continued despite all therapy, and the patient expired some twelve hours later. Post-mortem lumbar puncture revealed clear spinal fluid with a normal cell count, and no organisms grew on culture.

At autopsy two hours after death, a large collection of air was found to occupy the whole of the anterior mediastinal space in the form of large blebs in the connective tissues. There was no air in the subcutaneous or fascial spaces of the neck. The thorax was opened under water, and no evidence of pneumothorax was found. The trachea and bronchi were quite patent, and although small ecchymotic areas were seen near the tracheal bifurcation (due to instrumentation), no perforation was detected. The heart and lungs were grossly normal.

Unfortunately, aspiration failed to relieve the mediastinal emphysema in this case, due no doubt to the extreme degree of pocketing of the air within the tissues of that region. As will be discussed later, such extreme degrees of mediastinal emphysema as were present here can result in marked respiratory and circulatory difficulties and even death in the absence of accompanying pneumothorax. However, other possible factors were considered. Although a blood serum carbon dioxide content was not done, enough sodium lactate was incorporated in the parenteral fluids to have corrected any acidosis which might have been present. The negative spinal fluid examination, while not absolute evidence, tends to rule out a coincidental encephalitic process. The Cheyne-Stokes type of

breathing, together with convulsive movements, coma, and generalized muscle rigidity, suggests that cerebral anoxemia played a major role in causing the patient's death. The massive mediastinal emphysema, acting just as does a valvular tension pneumothorax, could have been responsible for this fatal chain of events.

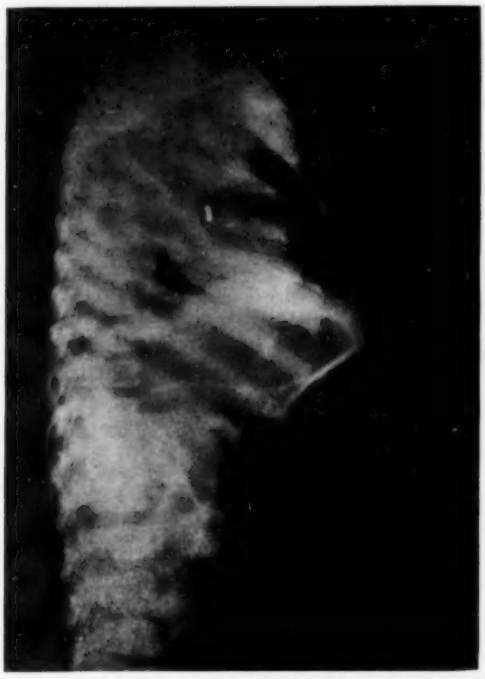
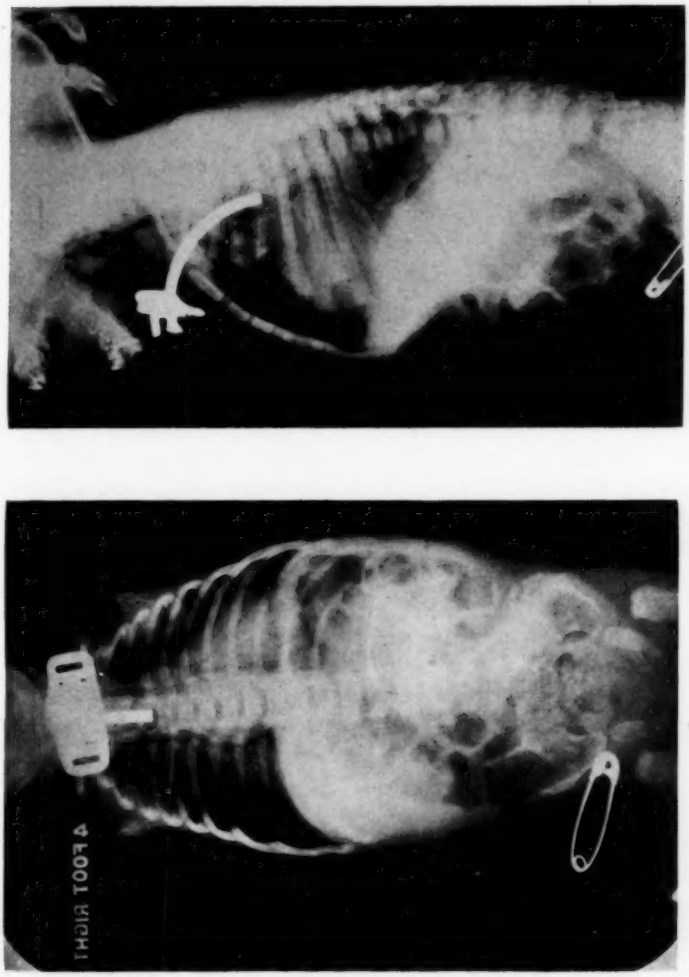


Fig. 1 (Case 3).—Lateral roentgenogram of the chest taken immediately post mortem, showing the collection of air in the anterior mediastinum.

CASE 4.—A 2-month-old white male was admitted to the St. Louis Children's Hospital on July 25, 1942, for treatment of a large congenital hemangioma of the soft palate. At this time the respirations were normal, as was physical examination of the chest. The tumor was large enough to obstruct the pharynx partially and thus had interfered with the infant's nutrition. Because of the possibility that it might swell sufficiently under treatment to cause respiratory embarrassment, a preliminary tracheotomy was performed. The procedure was a very difficult one, owing to the small size of the patient and to the constant struggling and crying that went on during the operation. On at least one occasion during the operation air was noted to bubble into the wound.

About twenty minutes after the operation, the baby became quite cyanotic and stopped breathing but was resuscitated with the aid of stimulants and carbon dioxide-oxygen inhalations. From that time on the respirations were noted to be very shallow in type, but no more episodes of cyanosis were observed. Examination of the chest three hours later revealed tympany and absent breath sounds over the right lung field, but no crackling sounds were heard over the percordium. Fluoroscopy confirmed the presence of a right pneumothorax with shift of the

mediastinum to the left, and in the lateral view revealed a large collection of air in the anterior mediastinum (Fig. 2). A needle attached to an oiled syringe was inserted into the right chest low in the midaxillary line, and the plunger of the syringe immediately rose to the 20 c.c. mark. The procedure was repeated later, and



B.

A.

Fig. 2 (Case 4).—Anteroposterior and lateral roentgenograms of the chest, showing mediastinal emphysema and right-sided pneumothorax. The former is quite striking in the lateral projection, but close inspection of the anteroposterior view shows the air about the heart and great vessels.

28 c.c. more of air escaped under pressure. A needle was also inserted into the anterior mediastinum under direct fluoroscopic vision, but only 5 c.c. of air could be obtained with the aid of suction. After these procedures, the right lung appeared completely expanded when viewed under the fluoroscope, but air could still be seen in the anterior mediastinal space. The baby's respirations now became normal in character, and at no time later did he suffer respiratory embarrassment. The air gradually disappeared from the anterior mediastinum over a period of three days, and pneumothorax did not recur.

While in this infant it was shown that the pneumothorax was definitely of the tension variety, the baby fortunately compensated for it fairly well. The one distressing period of cyanosis and apnea probably marked the onset of pneumothorax and mediastinal emphysema, and this episode might easily have been fatal had the tension in the pleural and mediastinal spaces risen high enough. It is entirely possible, however, that had aspiration not been performed, the air in the pleural cavity would have been reabsorbed in time. But the difficulties incident to maintaining an adequately functioning tracheotomy tube in so small a baby make it imperative that any complicating factors (such as pneumothorax) be removed.

DISCUSSION

Mediastinal emphysema can apparently occur in a variety of situations. First, there are those conditions associated with violent respiratory efforts, such as obstetric labor, pertussis, and obstructive tracheobronchitis.[10] The mechanism here, as in the cases secondary to compression injuries of the thorax and those occurring in newborn infants, is presumably that of alveolar rupture with subsequent development of interstitial pulmonary emphysema and dissection of air along perivascular and peribronchial sheaths to the mediastinum.[10, 11] Next, in any situation whereby the cervical fasciae are opened, such as penetrating neck wounds, thyroidectomy, or operations about the jugular vein, air gains easy access to the mediastinal spaces. This was recognized as long ago as 1882 by Champneys.[8] He performed tracheotomies on stillborn children and found that mediastinal emphysema was frequently produced when vigorous artificial respiratory efforts were instituted, *providing entry of air into the trachea was impaired.* Finally, perforation of the esophagus or the trachea offers still another pathway and has been observed experimentally to produce mediastinal emphysema.[12]

Mediastinal emphysema alone can produce serious effects. Fall in blood pressure, pulmonary edema, pericardial effusion, and death by cardiac tamponade were noted by Ballon and Francis following the introduction of air into the mediastinum of the rabbit.[12] However, when accompanied by tension pneumothorax, the probability of a fatal outcome was definitely increased. Even though no tears in the mediastinal pleura could be demonstrated in these animals, it was assumed that air did rupture it to reach the pleural cavities, for in several experiments positive intrapleural pressures did not occur until the intramediastinal pressure had risen significantly.

In addition to the above, tracheotomy provides several other possible routes for the entry of air into the mediastinal and pleural spaces. First, could there take place a rupture of lung parenchyma with the production of pneumothorax directly? Instances of nontuberculous

spontaneous pneumothorax occur in this manner. There have been shown to be potential spaces in the subpleural zones which communicate with the alveoli, and these "spaces" can dilate enormously under stress to rupture the pleura.[10] Next, direct injury to the pleural domes at time of operation is a possibility. Frequently a bulging forth of tissue, supposedly pleura, and rushes of air are noted during the course of tracheotomy, and this was definitely observed in the last three of our cases. However, in two of our cases the pneumothorax was bilateral, necessitating injury to both pleural domes. If either of these routes operated, the mediastinal emphysema would be secondary to the tension pneumothorax, via rupture of the mediastinal pleura. This has been observed following artificial pneumothorax.[10]

Granting these possibilities, the mechanism which seems most plausible in our cases is that of suction of air into the mediastinum via the deep cervical fascia. From there it may rupture through relatively thin parietal pleura to produce unilateral or bilateral pneumothorax. The assumption that the pneumothorax in our cases occurred in this manner is being made because of the fact that histologically the mediastinal pleura in children is known to be thinner and less dense than that of the adult[13] and because a considerable decrease in intrathoracic pressure results from violent inspiratory efforts in the face of an inadequate airway (the tracheal obstruction for which the tracheotomy is being done). The development of tension within the mediastinum is dependent on a "ball-valve" mechanism, by which air sucked into the mediastinum cannot escape unless it ruptures into the subcutaneous, retroperitoneal, or intrapleural spaces. Thus, it is conceivable that the production of a pneumothorax might actually relieve the patient temporarily through reduction of intramediastinal pressure. But if air continues to be drawn into the pleural spaces, this same "ball-valve" mechanism will produce a tension pneumothorax (see Case 2). The resulting respiratory embarrassment is sudden and quite severe and all too frequently is fatal.

It is entirely possible that many more cases of mediastinal emphysema occur following tracheotomy than are recognized. The symptoms of pneumothorax may even be such as to simulate a mucus-filled tracheal cannula, as did those in our fourth case. If sufficient tension is not produced within the mediastinal or pleural spaces, objective signs will be lacking. While the diagnosis of pneumothorax is not difficult by physical examination, that of mediastinal emphysema is best made by fluoroscopy in the lateral view, although at times peculiar crackling sounds may be heard over the precordium.

Treatment *must be immediate* in those infants with well-marked symptoms, as our cases demonstrate well the suddenness with which death can occur. Aspiration of air from the pleural cavity is indicated and may be a lifesaving procedure where the symptoms are marked. This may

have to be repeated if symptoms of respiratory distress recur, and closed drainage of the chest may be necessary as a more permanent safety measure.[9, 10] The relief of massive mediastinal emphysema is more difficult, as evidenced by our third and fourth cases, due to pocketing of air among the loose connective tissues. Surgical exposure of the anterior mediastinum and application of suction devices to the deeper tissues of the lower neck regions have been employed with only occasional success.[10]

Since the *combination* of tracheal obstruction and severe respiratory efforts tends to favor the development of mediastinal emphysema and pneumothorax during tracheotomies in children, a logical method of prevention is suggested: Preoperative intubation or insertion of a bronchoscope should be of definite value because either offers an adequate airway during the operation. Michels advocates the use of a bronchoscope as a routine procedure in tracheotomy. Also, our cases illustrate still another good reason for performing tracheotomy early; that is, as soon as adequate indications arise, instead of waiting until it must be done as an emergency.

SUMMARY

1. Four cases of mediastinal emphysema and/or pneumothorax following tracheotomy are presented.

2. Three of the cases were fatal, and in two of the fatal cases these complications were the immediate cause of death. In the third case they were definitely contributory.

3. Such complications may be sudden and unanticipated and may occur during tracheotomy or shortly thereafter. Immediate careful examination of the chest, preferably by fluoroscopy, is recommended in all post-tracheotomy cases in infants exhibiting circulatory or respiratory embarrassment. Aspiration of the air should be performed at once.

4. Many instances of post-tracheotomy mediastinal emphysema and probably some of pneumothorax go unrecognized for lack of striking symptoms.

ADDENDUM

Since submission of this paper for publication, we have observed ten additional young children with mediastinal emphysema following tracheotomy for acute laryngotracheobronchitis. Four had pneumothorax. Six of these children, including one in whom pneumothorax occurred, exhibited no symptoms attributable to these complications and were diagnosed by incidental x-ray examination. The air disappeared spontaneously in from two to fifteen days. In only one instance did we observe characteristic physical signs. In the other four children these complications produced marked respiratory distress and apparently contributed to the three deaths which occurred. In two of the fatal cases unilateral tension pneumothorax was present, while in the third, massive mediastinal and retroperitoneal emphysema developed. These findings were confirmed at autopsy in each case. Since these children were

suffering from severe respiratory infections and the post-tracheotomy complications developed during the night, there was an unfortunate delay in carrying out measures for mechanical relief. The single patient who survived had immediate relief from pleural aspiration, and pneumothorax did not recur.

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HEMOPHILUS INFLUENZAE TYPE B LARYNGITIS WITH BACTEREMIA

Report of Four Cases

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SINCLAIR[1] first described this syndrome comprised of acute laryngitis and bacteremia produced by *H. influenzae* type b. He reported ten cases. There is one case reported by the French.[2] Because it is evident that this disease is much more common than this would indicate and because a prompt diagnosis is important, we are reporting four additional cases.

The interest in *H. influenzae* type b dates from Pittman's work[5] in which she demonstrated that this substrain was the most virulent of the several of the organism. Type b was the only strain isolated from the spinal fluid in meningitis, and it has been demonstrated as the causative organism in septicemia and laryngitis.

Alexander[4] suggested the rapid identification of the organism by a typing procedure similar to the Neufeld method, using material obtained by swab direct from the nasopharynx and typing it against *H. influenzae* type b rabbit antisera. Capsular swelling of the organism indicates a positive typing.

The clinical picture described by Sinclair[1] is so definite that being familiar with it one could scarcely overlook the diagnosis. Three of our patients were diagnosed on observation before reports of cultures were available. The other patient was seen before Sinclair's article appeared. All four patients showed almost pure cultures of *H. influenzae* type b from the pharynx and pure cultures of the same organism from the blood.

All four of them fulfilled the criteria as set down by Sinclair for diagnosis of this syndrome. These are: (a) acute onset; (b) extreme prostration or "shock" out of all proportion to the local observations; (c) laryngitis of severe degree with marked edema and hyperemia of both the false and true vocal cords; (d) fever and neutrophilic leucocytosis of marked degree; (e) positive throat culture and bacteremia of *H. influenzae* type b.

Recovery following tracheotomy and adequate sulfonamide therapy was rapid and dramatic in the three patients so treated. The other child who did not have a tracheotomy performed had a much more prolonged course which was complicated. We are presenting these cases to emphasize the emergency nature of this syndrome.

From the Children's Memorial Hospital.

CASE 1.—R. M., a 4½-year-old boy, acutely ill, entered the hospital Jan. 7, 1940. He had had an upper respiratory infection one week previously but had apparently recovered. The onset of this illness was sudden. At 3 A.M. he awakened out of a sound sleep with difficulty in breathing, slight elevation of temperature, earache, and upper chest pain. Four hours later respirations became labored with inspiratory and expiratory stridor. The condition became progressively worse until admission late in the day of the onset.

The family and past medical history were noncontributory.

Physical examination revealed an extremely ill child who was listless, "knocked out," dusky in color, and who had stridor with substernal retraction. The throat was hyperemic, but no membrane was present. The lungs were resonant throughout, and there were no râles heard, although some suppression of breath sounds was suspected over the right lower lobe.

The admission temperature was 105° F. He was placed immediately in a steam room, but after no apparent improvement, in one and one-half hours oxygen was started. Respirations became less labored and there was less retraction. The temperature dropped to 101.8° F. On the following morning the patient was restless and irrational. The temperature again rose, to 106° F. this time. Sulfapyridine, ½ Gm. every four hours, was then started but was discontinued in twenty-four hours because of vomiting. For forty-eight hours beginning January 8 the patient's temperature remained above 104° F., and at one time reached 107° F. despite vigorous physical measures as well as oral salicylates to reduce it. By January 10 there appeared to be some improvement. The immediate response was thought to be due to the injection of 40 c.c. of convalescent scarlet fever serum given intramuscularly the evening of January 9. Fluids had to be maintained by intravenous methods. On January 11 sulfapyridine was again started in the same dosage as before. On this date the admission blood culture was reported to be a pure culture of *H. influenzae* type b. The same organism was also isolated in pure culture on chocolate agar from a throat swab. Broth cultures of the material from the pharynx revealed pneumococci types VI and XXI and a few streptococci. Repeat cultures of the throat yielded numerous type XIII and type XXI pneumococci and a few colonies of *Streptococcus hemolyticus*. Direct Neufeld typing of the throat swab yielded pneumococcus type VI and two other types which are not identified. Although the patient was somewhat better on January 11, he still was semistuporous. Improvement continued with gradual reduction of fever to 100° F. on January 13, but a rise began again on the following day. Physical examination at this time revealed dullness and suppression over the left base which was believed to be due to fluid, an impression substantiated by x-ray films. Two 200 c.c. transfusions of whole blood were given without reaction and by January 19 x-ray films showed some clearing of the process in the left chest. The temperature gradually returned to normal and the patient made a slow recovery, being discharged on the thirty-fourth hospital day. A total of 59 Gm. of sulfapyridine in doses of ½ Gm. every four hours was given. The admission blood count was hemoglobin, 15 Gm.; red cells, 5.55 million; white cells, 20,200—polymorphonuclear leucocytes, 68; lymphocytes, 24; monocytes, 6; eosinophiles, 2. January 15 the hemoglobin was 11 Gm., the red cells were 3.6 million, the white cells were 24,000, the polymorphonuclears were 84, and the lymphocytes were 16. The white cell count remained elevated until the sixteenth hospital day when it was 9,650, with 55 polymorphonuclears and 45 lymphocytes. The red cell count was still low, which was thought to be due to the sulfapyridine. This child has been followed in the outclinic and apparently has had no residual except for some suppression of the breath sounds over the left base for approximately three weeks after discharge.

CASE 2.—F. B., a 2-year-old white male, entered the hospital Aug. 19, 1942. For three days prior to admission the patient had had a slight nasal discharge, and at 11 A.M. the day of admission he complained of malaise which was shortly followed by difficulty in breathing. Respirations rapidly became more labored and vomiting occurred once. By 6:30 P.M. his dyspnea was extreme; there was marked stridor and fatigue. The child appeared completely exhausted and was listless and apathetic.

Family and past histories were noncontributory.

Physical examination revealed a fairly well-developed and nourished boy. He was suffering definite respiratory distress, was slightly cyanotic, and had marked substernal retraction with inspiratory stridor. He demonstrated the picture of shock alluded to above. The pharynx was injected and a profuse mucopurulent discharge from both nares was observed. The cervical nodes were bilaterally enlarged and tender. Direct visualization of the larynx revealed a markedly edematous and inflamed epilgottis which was difficult to elevate because of the intense swelling. The arytenoids and aryepiglottic folds were similarly involved. The false cords were so edematous that the true cords could not be seen without the aid of the bronchoscope. The true cords were subsequently seen to be fairly pale and little involved in the process.

An immediate tracheotomy was performed with complete relief of the respiratory distress. The patient's color improved and he appeared to lose all of his apprehension. Sulfathiazole was started by mouth. The admission temperature was 102.2° F. and rose to 103.5° F. postoperatively but was 100° F. the following morning. Cultures of the blood, throat, and tracheal secretions showed *H. influenzae* type b in pure culture in all but one specimen. *Streptococcus viridans* was also isolated from the culture taken from the trachea at the time of operation. The postoperative course was uneventful. Pharyngoscopy on the second postoperative day revealed little change in the edematous condition of the epiglottis, but the examination on the fifth day revealed that the epiglottis was still red and swollen but that the airway was patent. The admission blood count was hemoglobin 11.5 Gm.; red cells, 3,870,000; white cells 18,500—polymorphonuclear leucocytes, 83; lymphocytes, 15; monocytes, 2. A total of 21.25 Gm. of sulfathiazole was given. The tracheotomy tube was removed the ninth day, and the child was discharged on the eleventh hospital day. He has since been followed in the outclinic and has made a complete recovery.

CASE 3.—R. K., a 23-month-old boy, had been perfectly well until six hours previous to time of admission. At this time he began to have severe laryngeal stridor which had been preceded by an attack of vomiting. His temperature was 101° F. and pulse and respirations were both elevated. He had been getting progressively worse until he was seen in the admitting room.

Physical examination revealed an acutely ill, listless, apathetic, fatigued child in obvious respiratory distress. His color was gray and he had an anxious facial expression. There was no cough, but there was marked retraction of the sternum and obvious laryngeal obstruction. There was some soft enlargement of the tonsillar nodes but no generalized lymph adenopathy. The throat was fiery red, but there was no membrane. The nose was moderately congested.

An immediate tracheotomy was done and the respiratory difficulty was relieved. Cultures from the nose, throat, and blood revealed *H. influenzae* type b in pure culture except for a few type IV pneumococci which were isolated from the nose. Sulfathiazole was started by mouth and recovery was rapid and without incident. The tracheotomy tube was removed on the ninth hospital day and the child was discharged on the tenth. Temperature was 101.2° F. on admission and rose to 101.6° F., but within twenty-four hours it was below 100° F. and never again exceeded that level. The admission blood count was hemoglobin, 13.5 Gm.; red cells, 4,860,000;

white cells 34,200—polymorphonuclears, 85; lymphocytes, 10; monocytes, 5. A total of 16.5 Gm. of sulfathiazole was given. At the time of discharge the patient was well.

CASE 4.—P. E., a 3-year-old white female, had a running nose for three days previous to the onset of her present illness but was apparently well Nov. 7, 1942. At 3 A.M. the following day she awoke with difficulty in breathing, sore throat, and inability to swallow. She vomited once and retched many times during the remainder of the night. The dyspnea did not subside during the day of November 8 and the vomitus contained some bright red-tinged mucus. At about 4:30 P.M. the patient's condition became suddenly worse. Dyspnea and retraction of the sternum and abdominal wall appeared. At this time the mother stated that the child was blue, listless, and seriously ill.

The family history was negative, but the past medical history revealed that the child had been previously hospitalized two days for a possible diphtheritic pharyngitis but had been discharged after negative cultures had been returned.

The physical examination revealed a somewhat cyanotic, listless, fatigued, toxic child who was in obvious respiratory distress. She had marked inspiratory difficulty accompanied by a wheeze. Expirations were slightly less difficult and were associated with a rumble. There was substernal retraction with each inspiration. Pulse and respiratory rates were both elevated. The throat was extremely red and there was considerable pus and mucus present in the posterior pharynx. Direct laryngoscopy revealed edematous, red, false cords and injection and swelling of the true cords. The airway was almost completely closed by the edematous laryngeal structures.

An emergency tracheotomy was done and a tube was inserted. The respirations immediately became easier, and substernal retractions ceased. Sodium sulfathiazole, 11.5 Gm. was given intravenously. The temperature at this time had reached 104° F. By the following morning the child's neck and the tissues of the lower jaw were markedly swollen. She was complaining of dysphagia at this time and refused to swallow. Intravenous fluids were necessary to maintain fluid intake. Sodium sulfathiazole, 1.5 Gm., was injected intravenously the following morning. The temperature remained above 101° F. throughout the second hospital day and then fell below 100° F. and remained there for the rest of the hospital course. Sulfathiazole was started by mouth as soon as she could swallow and was continued until the eighth day, a total of 17 Gm. being given. The recovery was uneventful.

The blood and throat cultures revealed pure cultures of *H. influenzae* type b. The blood count on admission showed a red cell count of 4,140,000; hemoglobin, 12.5 Gm.; white cell count, 21,800—polymorphonuclears, 86; lymphocytes, 14. The tracheotomy tube was removed on the twelfth day and the child was discharged on the fifteenth. She has since been seen once in the outclinic. Her voice is unimpaired, and breathing is normal.

DISCUSSION

Several points in the picture stand out clinically: (1) This condition is more common in preschool children. (2) The onset is so sudden that it can be dated to the hour. (3) Marked prostration defines the patient's condition as opposed to that found in ordinary croup. (4) The temperature is elevated, but drops with operative procedure and chemotherapy. The early surgery seemed to accelerate recovery in our patients, for, in the one unoperated case, the temperature remained elevated for several days despite chemotherapy. (5) In all patients there was a marked leucocytosis with an absolute polymorphonuclear in-

crease of marked degree. (6) Blood and throat cultures showed an almost pure growth of *Hemophilus influenzae* type b in all four cases. (7) The early establishment of an adequate airway apparently shortens the course of the disease as well as its severity. It is a life-saving procedure in some instances.

The differential diagnosis in this condition must consider the following entities: (1) In ordinary *catarrhal croup* the child is much less toxic than in the *H. influenzae* type of laryngitis. (2) *Foreign body* can usually be excluded by history as well as time of onset. (3) *Diphtheria* can be ruled out on the absence of a membrane plus negative smears and cultures of laryngeal secretions for the Klebs-Löffler organism. The patient is usually not as toxic or fatigued as the *H. influenzae* patient. (4) *Postpharyngeal abscess* can be determined by digital examination and history of slow onset with considerable preceding acute pharyngitis. (5) *"Thymic attacks"* sometimes produce symptoms but are not febrile and patient is not toxic. (6) *Acute edema of the larynx* from other causes can be ruled out bacteriologically only, but none give the picture of profound debility that this infection produces. (7) *Laryngismus stridulus* is a dangerous diagnosis to make at best. The presence of rickets and spasmophilia help point to the etiology of the spasm. (8) Occasionally the *rupture of a caseous bronchial or mediastinal node* into the trachea or bronchus will simulate laryngeal obstruction. Examination of the lungs and expectoration of the caseous material will make the diagnosis. (9) *Pertussis* may occasionally give the picture of obstruction but should be readily differentiated by history and clinical picture of paroxysmal cough over a long period of time.

CONCLUSION

1. Four cases of *H. influenzae* sepsis with laryngitis are reported.
2. The beneficial effect of early tracheotomy is emphasized.

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SUDDEN DEATH IN INFANTS DUE TO PNEUMONIA

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PNEUMONIA has been alluded to in the literature from time to time as a possible cause of sudden death in infants previously thought to be essentially well, but the importance of the pulmonary lesion has not as yet received proper recognition. For instance, no mention of pneumonia is made in the most recent editions of the standard textbooks on pediatrics under the title of Sudden Death. It is stated in *Holt's Diseases of Infancy and Childhood*, however, that sudden death "is not a very uncommon occurrence in infants who are apparently healthy"; and that, "in very young infants, a fatal infection may run its course without producing noteworthy symptoms, even without fever." Although little emphasis is accorded to pneumonia, careful pathologic and bacteriologic studies have shown this to be the cause of sudden death in the majority of cases analyzed. In discussions centering about the role of the thymus gland in sudden death, both Farber[1] and Goldbloom and Wiglesworth[2] refer to the role of pneumonia in sudden death in infancy. The latter authors found nineteen of thirty deaths attributable to definite inflammatory lesions in the lungs. They state, "It is suggested that many cases of sudden death, although not all, are caused by fulminating infections, possibly associated with immature immunity on the part of the infant. The lesions commonly found are an interstitial pneumonia and a peribronchitis." Neely[3] recently reported the autopsy findings in three infants with cardiac enlargement due primarily to interstitial pneumonitis. One of these infants died suddenly with no history of previous illness. Waldblott,[4] writing on the pathologic changes in thirty-four cases of "thymic death," concludes, "The most constant and characteristic changes were present in the lungs."

At the last meeting of the American Association of Pathologists and Bacteriologists, Werne emphasized the occurrence of pulmonary lesions in a group of fifty infants dying unexpectedly. In an abstract of his paper[5] he states, "The majority of sections of lung showed the occurrence of bronchitis, peribronchitis, and peribronchial pneumonitis; mononuclear cells predominating."

Brief accounts of three cases of sudden death resulting from pneumonia are presented here to emphasize this relationship.

CASE 1.—A female infant, 3½ months old, was found dead in her crib at nine o'clock in the morning on February 20. She had appeared to be well when seen by the nurse earlier in the morning, at which time her temperature was recorded as normal. This patient had been transferred to the Minnesota Home Society from

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the Booth Memorial Hospital on February 12. On that date, four infants in the latter institution presented their first symptoms of pneumonitis in the first of two epidemics of primary virus pneumonitis reported by me.[6, 7]

Necropsy Findings.—The pleural cavities showed no excess fluid and no adhesions. The right and left lungs weighed 65 and 50 Gm., respectively. The pleural surfaces had a mottled appearance and in the parenchyma there were small areas

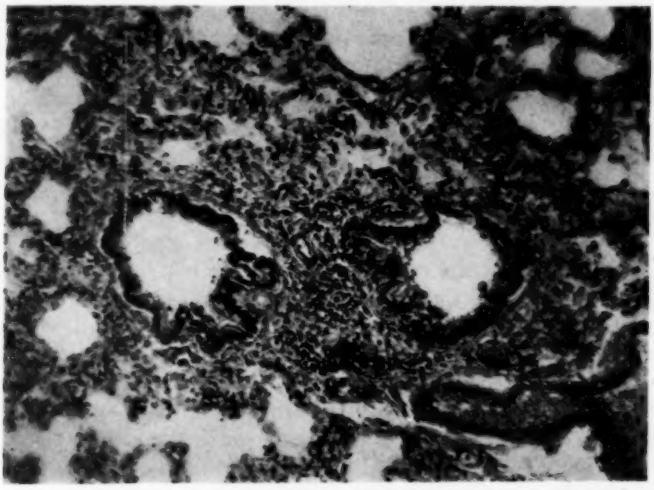

Fig. 1.—Photomicrograph showing small round cell infiltration about bronchioles, with edema and hemorrhage in surrounding tissues.

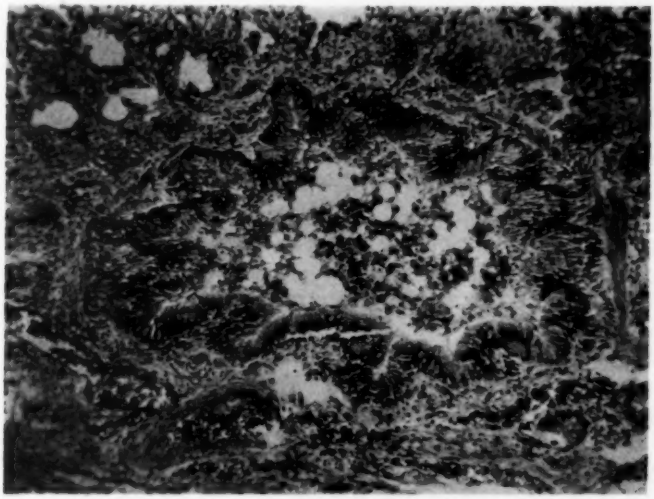

Fig. 2.—Photomicrograph showing bronchus with epithelial exudate, no polymorphonuclear leucocytes or bacteria. Hemorrhage, edema, and small round cell reaction are also demonstrated.

of hemorrhage; frothy mucuslike fluid exuded from the bronchi. There were no macroscopic areas of definite consolidation. The bronchial mucosa was congested and edematous.

Microscopically the most significant alteration was the infiltration of small round mononuclear cells about the bronchial and bronchiolar system. Diffuse hemorrhage within the alveolar spaces with thickened edematous septa stood out as an additional feature. Many small bronchioles appeared collapsed. Some contained an epithelial cell exudate with no evidence of leucocytes or bacteria (Fig. 1).

CASE 2.—A male infant, 2 months of age, was normal until the day before death, when slight nasal discharge and cough were noted. The temperature was normal. Feedings were taken well. At 3 A.M. the patient was found to be extremely dyspneic and cyanotic and died shortly after his condition was discovered by the nurse.

Necropsy Findings.—The pleural cavities contained no free fluid or adhesions. The right lung weighed 100 Gm.; the left, 110 Gm. A small amount of exudate was expressed from the bronchi. There were scattered red areas throughout the lung parenchyma. The liver weighed 250 Gm. On section, fatty changes were seen. Microscopic examination of the lungs showed scattered areas of congestion with marked thickening of alveolar septa. Large patches of mononuclear cells and numerous red blood cells were seen throughout the affected areas. No leucocytes or bacteria were present in the exudate of the bronchi, the latter being made up almost entirely of epithelial cells. No inclusion bodies were found in the intact cells (Fig. 2).

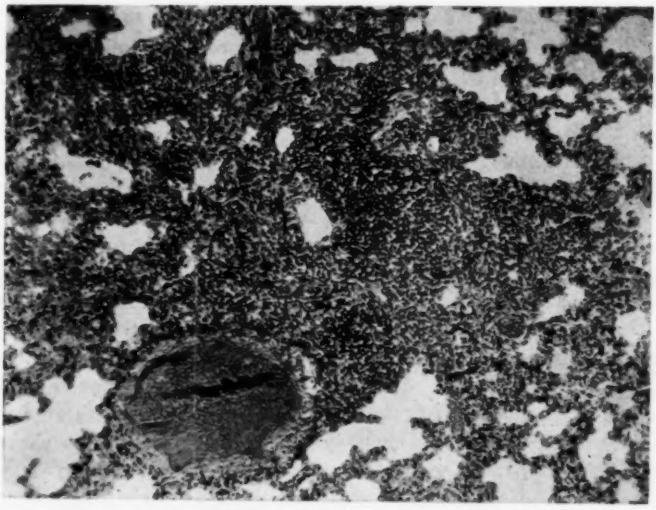

Fig. 3.—Low-power photomicrograph showing patches of small round cells scattered throughout affected tissues.

CASE 3.—A male infant, aged 5 months, was well until two days before death, when a slight nasal discharge and cough were recorded. On the day of death, he was bathed, took the 10 A.M. feeding well, and was put to bed. Although he appeared well and happy at 11 A.M., he was found dead in the crib at 11:45 A.M. with frothy reddish mucus in the nose and throat. There was no evidence of food aspiration.

Necropsy Findings.—The right lung weighed 80 Gm.; the left, 70 Gm. Lumpy areas of consolidation were noted and the pleural surfaces appeared red. On section, the cut surface was dark red and a large amount of bloody frothy mucus exuded from the bronchi.

Microscopic examination showed a diffuse hemorrhagic congestion in the involved alveolar areas. The septa were thickened with mononuclear cellular elements, edema, and hemorrhage. Scattered areas of small round mononuclear cells were seen. No polymorphonuclear leucocytes or bacteria were seen in the exudate (Fig. 3).

COMMENTS

The pathologic pulmonary reaction found in these cases of sudden death in young infants previously considered to be well was similar to that reported by McCordock and Muckenfuss[8] and Sprunt[9] in experimental animals. At necropsy there was evidence of widespread congestion of the lung with diffuse hemorrhage and scattered areas of mononuclear infiltration or proliferation. In discussing the nature of virus pathology, Rivers[10] says, "the fact that inflammation occurs in many virus diseases cannot be denied, and, despite the acute nature of some of the diseases, if secondary infections do not intervene, the inflammatory process is usually characterized by an infiltration of mononuclear cells." Sprunt[11] states that "in virus diseases the mononuclear reaction occurs in the acute phase of the disease and in others as pneumococcus pneumonia in the stage of resolution."

The three cases briefly reported here occurred in association with the first epidemic of virus pneumonitis referred to previously.[6] Pathologically there was a close similarity between the picture presented by the infants in these cases and that seen in the infants with fatal cases of virus pneumonitis. Although none of the present patients showed the typical cytoplasmic inclusion bodies seen in the bronchial epithelium of the latter, it is possible that sudden death preceded the formation of inclusions. McCordock and Muckenfuss,[8] using vaccinia virus, demonstrated that the pneumonitis in experimental animals varies with the quantity of virus used. The concentrated dose produces an acute hemorrhagic type of histologic response with necrosis, whereas the more dilute dose produces a proliferative response in the alveoli with mononuclear cellular infiltration. The most outstanding and constant histopathologic change in the infants whose cases are presented here was the interstitial mononuclear response in the alveolar tissues, as shown in Fig. 3. This was likewise the predominant cellular response found at autopsy in the infants in our cases with primary virus pneumonitis, most of whom died on the sixth or seventh day of illness. All of the latter patients showed, in addition, proliferation and desquamation of bronchial and bronchiolar epithelium and also cytoplasmic inclusion bodies in these cells.

The absence of bacteria and the almost complete lack of a polymorphonuclear leucocyte response in the infants in the present cases suggested a virus etiology. Additional evidence in favor of this assumption

is afforded by the fact that the marked mononuclear infiltrations demonstrated in the microscopic sections were similar to those observed in experimentally produced, as well as spontaneously occurring, virus pneumonitis.

SUMMARY

1. The clinical and post-mortem findings in three infants dying suddenly without previous evidence of illness are presented.

2. The only significant pathologic change found was a marked interstitial mononuclear pneumonia associated with diffuse pulmonary hemorrhages and edema.

3. It was pointed out that pneumonia is probably the most important single cause of sudden death in infancy.

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WHEAT GERM OIL (VITAMIN E) IN THE TREATMENT OF CONGENITAL NONOBSTRUCTIVE HYDROCEPHALUS

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NUMEROUS methods of therapy, nonsurgical and surgical, some of them very ingenious, have been suggested in the past for the treatment of this disorder. The nonsurgical methods were aimed primarily at the dehydration of the central nervous system through repeated lumbar punctures,[1] the use of hypertonic solutions intravenously or rectally,[2] or the administration of the xanthine group of drugs for the purpose of increasing elimination of fluids through the urinary system.[3] None of these methods have proved satisfactory except in isolated instances.

The surgical procedures in most patients followed Dandy's[4] original method of destroying the choroid plexus in the ventricles or Heile's[5] ingenious but unsatisfactory operation of ureterodural anastomosis. Dandy's operation has been modified by Putnam[6] and Scarff[7] by substituting electrocoagulation for actual resection of the plexus. While the operation entails a high operative mortality,[8] the results in Putnam's larger series of cases have appeared to offer fair success in selected cases. Whether the arrest of the hydrocephalus was due directly to the destruction of the plexus or was caused by a readjustment for the better of the hematoencephalic barrier as a result of the operation is uncertain. It is known, however, that occasionally an arrest of a progressive hydrocephalus does occur through a spontaneous adjustment of the spinal fluid secretion absorption mechanisms.

PATIENTS TREATED

The present investigation began when a patient with a case of progressive hydrocephalus, associated with spina bifida, Fröhlich's syndrome, and dystrophic musculature of lower extremities, was placed on vitamins E and B in May, 1940. A gradual decrease in size of the spina bifida, arrest of hydrocephalus, and a reduction in the rubbery texture of extremities were observed after this patient remained under treatment for a period of three months. Eight other patients with various degrees of hydrocephaly have been placed under treatment since. Five of these patients were male and four were female. The oldest child was 2 years of age when first seen and the youngest, 8 days. One of the patients had spina bifida occulta and four others had meningoceles of varying sizes associated with the hydrocephalus. The locations of the meningoceles were as follows: One was located in the cer-

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vical area, one in the thoracolumbar region, and the others in the lumbosacral spine. All the children with spina bifida except the one with the cervical meningocele had extensive paralysis of lower extremities associated with varying degrees of anesthesia.

METHOD OF TREATMENT

The children under treatment received a mixture of wheat germ oil,* and vitamin B complex,† one part of oil to four parts of vitamin B complex. The initial dose was 4 c.c. of this mixture, three times daily for children 2 years and over, and 2 to 4 c.c. daily for infants. The medication was either mixed with the feedings of the infants or administered with a medicine dropper and was well tolerated by all children when given in this form. The dosage was increased or decreased with the progress of the child by varying the concentration of the oil in the mixture. No unpleasant reactions have been observed from its administration except for a rare scarlatiniform rash on one occasion which disappeared with the decrease in dosage of the vitamin mixture. One child has received this medication regularly for two years and another for eight months with continuous beneficial effect. Vitamins A and D in maintenance doses in the form of vitamin concentrates or malt mixtures was also administered whenever it was found indicated.

ANALYSIS OF CASES AND RESULTS

The initial improvement in the treated patients was manifested by an increase in alertness of the child, gradual disappearance of bulging of fontanels, diminution of nystagmus wherever it was present, increase in muscle strength and ability to hold up head in instances where the child was unable to do so formerly. In several patients with hypertrophied lower extremities with a muscle texture resembling that of pseudohypertrophic muscular dystrophy, a gradual disappearance of the exudate took place with reduction in circumference of legs and thighs. In one patient with hydrocephalus with an extensive broken down meningomyelocele, involving the lower thoracic and lumbar spine and associated with cerebrospinal fluid rhinorrhea and paralyzed lower extremities, complete healing of the broken down sac took place, the rhinorrhea disappeared, the fontanels became closed, the circumference of skull failed to enlarge, and the lower extremities assumed a more normal texture.

In three instances of hydrocephalus associated with nystagmus and optic atrophy where previously no reaction to visual stimuli was observed, the nystagmus appeared less marked, the rapid progression of increase in skull circumference ceased and visual responses became apparent in that these patients were seen to reach out for objects held in front of them. All three patients showed increase in alertness, were

*Eli Lilly and Co.
†Lederle Laboratories, Inc.

able to move their extremities better, and hold up their heads when placed in a sitting position which they could not do formerly.

In two cases of meningocele with early hydrocephalus the patients were placed on vitamins E and B immediately following operation. No hydrocephalus developed in these patients and they have continued to gain since the operation, although some bulging of fontanels was observed preoperatively and there was discharge of spinal fluid from the meningocele sac.

CASE REPORTS

CASE 1.—A 2-year-old boy, P. B., was admitted to the Elliot Hospital on May 7, 1940. Patient was born with an extensive meningocele which extended from 5 D to sacral area. Gradual enlargement of head continued from birth so that at time of admission the circumference of skull was 22 inches. The physical findings included enlarged skull with open fontanels, clear, watery nasal discharge resembling spinal fluid, and extensive meningocele with a broken down surface exuding spinal fluid. Veins of scalp appeared dilated, eyeballs were turned down with nystagmoid movements of both eyes; flaccid paraplegia of both lower extremities with loss of sensation extending from 5 D down. Penis was microscopic, testicles pinhead size, and fat distribution of Fröhlich's type. Lower extremities were enlarged with rubbery texture of musculature. Patient was unable to sit up without support or hold up his head. His intelligence appeared to be that of a 6-month-old child.

He was given a mixture of vitamins E and B, 1 part of wheat germ oil to 3 parts of vitamin B complex, receiving 4 c.c. of the mixture three times daily. On May 27 the patient was able to hold up his head and sit up when supported. On June 27 he was able to sit up alone, responded better to visual and auditory stimuli; circumference of skull was 21¼ inches. Texture of legs appeared less rubbery and nystagmus disappeared. When rechecked again six months later, while continuing on same medication, his legs had lost rubbery texture, he was able to hold his head up well, was able to turn over and change position, and some movement reappeared in left leg. He was also able to say a number of words. The meningocele was covered with normal skin and rhinorrhea ceased.

One year later he was able to feed himself, called the examiner by name, was able to change position voluntarily. Skull circumference did not increase and fontanels were closed. He has continued to take the mixture of vitamins E and B, 1:7, 4 c.c. once daily.

When rechecked on Oct. 14, 1942, the skull circumference remained unchanged. Meningocele area was covered with normal skin. No appreciable movements were observed in lower extremities, although the intracutaneous and subcutaneous exudates have disappeared and their texture appeared normal. His intelligence has improved considerably, according to observations of nurse and mother, and during the examination he appeared alert and displayed much spontaneous interest which he did not exhibit during previous visits.

CASE 2.—An 8-month-old boy, T. S., was first seen at the Manchester Crippled Children's Clinic on Aug. 6, 1940, because of gradual enlargement of head circumference since birth and inability of patient to hold up his head. Two attacks of convulsive seizures occurred before admission to the clinic. On examination skull circumference was 22 inches. Patient displayed a typical hydrocephalic facies; his head drooped when he was placed in a sitting position, fontanels were wide open. Pupils were contracted with bulbs turned downward. Lower extremities showed poorly developed musculature with little voluntary movement.

He was given vitamins E and B, 1:4 mixture, 4 c.c. daily. Six months later he was able to take several steps. When rechecked at 18 months of age, he walked well, muscle tone had improved, and he had no difficulty in holding up his head.

At 2 years of age the fontanels appeared closed. Skull circumference was still 22 inches. He showed normal muscle tone at this time. Mentally he appeared within normal limits. He had no recurrence of convulsions.

CASE 3.—A 3-month-old child, L. L., was first seen at the Crippled Children's Clinic at the Elliot Hospital on Nov. 26, 1941, because of nystagmus, downward bulging of eyes, gradual enlargement of head, and inability to hold up head. Circumference of patient's skull was 17 inches; vision appeared defective in that she failed to respond to light flashed in her eyes or reach out for objects. Both discs appeared pale as a result of optic atrophy. There was a horizontal nystagmus associated with nodding tremor of head. Musculature of lower extremities showed a rubbery texture although all movements were present. Deep reflexes were increased generally, but no abnormal reflexes were present. Patient's mother refused to place the child under treatment at this time. When the child was returned to the clinic on Dec. 31, 1941, the skull circumference was 18½ inches, a gain of one and one-half inches in one month. The child did not respond to visual stimuli at this time, fontanels were bulging, and the nystagmus was more marked. There was little evidence of voluntary movement and when placed in a sitting position she was unable to hold up her head. Patient was placed on E and B vitamins, 1:7 mixture, 4 c.c. daily. On Feb. 10, 1942, circumference of skull was 19 inches, nystagmus was less marked, and she was able to hold head up well. On April 24 circumference of skull was 19½ inches. Child appeared more alert, responded normally to stimuli for a child her age. Musculature of lower extremities appeared more normal in texture. The child remained without medication till June 16. On that date the skull circumference was 20 inches. Nystagmus was greatly reduced and nodding tremor of head disappeared entirely; fontanels were closing in. She was also making attempts at standing up and was able to hold up head satisfactorily. She was again given a mixture of vitamins E and B. On November 30 she was walking without support, was able to repeat a number of words, and vision as far as could be determined was within normal limits.

CASE 4.—A 10-month-old child, L. G., was admitted on May 20, 1941, to the Elliot Hospital for operation for cervical meningocele. On admission the fontanels were open; skull was hydrocephalic and dolichocephalic. A soft purplish mass 3 inches by 2 inches protruded over lower cervical and upper dorsal vertebrae and was soft and fluctuating. Patient was unable to hold up head. Musculature of lower extremities showed rubbery texture but no paralysis was present. Reflexes were present and active, and there were no sensory changes.

X-ray of spine showed malformation of upper seven dorsal vertebrae and lower two cervical, with incomplete posterior arches, and irregularities of development.

The cervical mass was removed by Dr. David W. Parker on May 24, 1941. The following is Dr. Parker's note of the operation. "Findings: Protruding mass, cystic, 3½ inches by 1½ inches cervical dorsal region over spine. Mass excised with elliptical incision down to dura which protruded through hiatus in spinal canal about 1 inch long. Dura divided and flaps sutured. Flaps and fascia reflected from sides and sutured over opening in spinal canal."

Patient made an uneventful recovery except for some evidence of meningeal irritation which persisted for several days and was relieved by sulfathiazole. He was given a mixture of vitamins E and B, 4 c.c. daily, while in the hospital, and continued with same therapy following discharge on June 6. On July 22 he was able to hold head up well, range of movements of extremities was increased, and there was no evidence of increase in intracranial pressure. He continued with 4 c.c. of the mixture daily. When rechecked on March 11, 1942, he held his head

up well, sat up alone, was able to turn over voluntarily, attempted to stand up, was able to say a few words; skull circumference had not increased.

CASE 5.—A 5-month-old boy, R. P., was first seen on April 6, 1942, at the request of Dr. O. E. Caron of Nashua, N. H. The child weighed 10 pounds when born and a gradual but progressive enlargement of head was noted since birth. Although he responded well to auditory stimuli, he failed to show any response when a bright light was flashed in his eyes. He was unable to hold up his head when placed in a sitting position and showed very little voluntary movement. Examination showed a 5-month-old infant appearing older than his age. Facies was hydrocephalic. Skull was 18½ inches in diameter. He did not respond to the stimulus of bright light, although he turned his head when a tuning fork was placed close to his ear. Discs were pale and there was a horizontal and rotatory nystagmus. Lower extremities appeared large, with a rubbery texture to soft tissues of legs. No actual muscle tissue could be felt, however, as the skin, subcutaneous tissue, and muscle appeared fused together. He was able to move his lower extremities feebly. Deep reflexes were increased but no abnormal reflexes were present.

He was given a mixture of vitamins E and B, 1:4, 4 c.c. once daily. On May 28 his mother reported that he appeared more alert, moved extremities better, and that the extremities appeared less rubbery in texture. Skull circumference remained unchanged. He was able to sit up in a chair when supported by pillows and hold up head.

On June 25 circumference of skull was 18¾ inches. Nystagmus was much less marked. There was further absorption of subcutaneous exudate of lower extremities so that loose connective tissue could be felt at this time.

On July 16 circumference of skull was 18½ inches; nystagmus was much less noticeable, although he still showed a tendency to roll eyes downward.

On August 20 circumference of skull was 19 inches. Fontanels were closing in. There was also a suggestion of his being able to perceive bright light. He continued taking 1:5 vitamins E and B mixture, 4 c.c. daily.

On September 17 circumference of skull was between 18½ and 19 inches. He was able to sit up well and hold up his head; mother felt that he could perceive when the lights were put on; he also was able to distinguish between various members of family by their voices. Legs had lost their rubbery texture and muscles and loose connective tissue could be felt underneath the skin. He continued with vitamins E and B mixture, 1:4, 4 c.c. daily.

On October 10 circumference of skull was between 19 and 19¼ inches; nystagmus was much less prominent and apparently there was definite perception of bright light. Mother reported continuous gain in physical strength and general alertness. He was given 1:3 vitamins E and B mixture, 4 c.c. daily.

When rechecked on December 26 skull circumference had remained unchanged. Extremities and abdomen displayed normal texture with disappearance of subcutaneous exudate which previously gave the appearance of obesity. He was able to repeat a few words and was reaching out for objects held out in front of him. This appearance of visual perception of other than bright objects has been of only two months' duration and, of course, very gratifying to the family who had been told previously that the child would remain blind.

CASE 6.—A 5½-month-old boy, C. I., was first seen at the Crippled Children's Clinic at the Elliot Hospital July 21, 1942, for gradual enlargement of head, drooping of head when he was held up, bilateral horizontal nystagmus, and failure to respond to visual stimuli. Gradual enlargement of head had been noticed for at least three months.

The neurologic findings included skull circumference of 18 inches, bulging of fontanels, pale discs, no response to bright lights, horizontal nystagmus, inability to hold up head, with nodding tremor of head, rubbery texture to lower extremities

with suggestion of pseudohypertrophy. Deep reflexes were increased, but no abnormal reflexes were present. The child was placed on vitamins E and B mixture, 1:7 parts, 4 c.c. daily.

On September 1 skull circumference was between 17¾ and 18 inches. He appeared slightly more alert, the nystagmus was also less marked, and the texture of extremities appeared less rubbery.

On October 13 skull circumference was 18¼ inches. He was able to perceive lights and follow objects with eyes. Held up head well. Continued receiving 1:5 vitamins E and B mixture, 4 c.c. daily.

On December 22 he was seen to reach out for objects dangled out in front of him, nystagmus was much less marked, he held head up well and, according to mother, he was able to distinguish between strangers and members of family. He continued to receive vitamins E and B 1:4 mixture, 4 c.c. daily.

COMMENT

Dandy[9] has suggested the possibility that in cases of nonobstructive hydrocephalus congenital malformation of the subarachnoid spaces prevented the normal absorption of the spinal fluid secreted by the choroid plexus and thus caused the production of the hydrocephalus. His experimental studies[10] pointed to the choroid plexus as the main secretory organ for the spinal fluid, and the good results obtained following surgical destruction of the choroid plexus were accepted as confirmatory of this fact. The finding by Davis[11] of a case of hydrocephalus associated with an hypertrophied choroid plexus helped to confirm this impression. On the contrary, Hassin[12] has pointed out that hydrocephalus can occur without a normal functioning choroid plexus and in several of his patients hydrocephalus occurred where the choroid plexus was malformed and sclerosed and apparently with no secretory capacity. In his opinion the choroid plexus played no part in the secretion of the spinal fluid and he offered the suggestion that most of the spinal fluid is derived from the tissue fluids of the brain and is discharged through the perivascular spaces into the ventricles and into the subarachnoid spaces. The function of the choroid plexus he considers absorptive rather than secretory, with this absorptive capacity limited to certain ingredients of the spinal fluid and thus resembled in function that of the kidney tubules. Marburg[13] has also suggested that the disturbance in the permeability of the hematoencephalic barrier was responsible for the increase in secretion of spinal fluid and that the hydrocephalus was produced by excessive secretion of spinal fluid rather than being due to defective absorption. Hassin[14] has also reported an hydropic condition of the entire brain in hydrocephalus and not limited to the ventricles and subarachnoid spaces. It is probable that the hydrocephalus is oftentimes only a partial manifestation of a generalized tendency toward fluid retention in the body. When this is present, as seen in several of our patients, the subcutaneous tissue and musculature of abdominal wall and extremities frequently acquires a rubbery texture because of this excessive intracellular and extracellular fluid accumulation.

Whether this disturbance in the secretion-absorption mechanism is due to endocrine factors such as disturbance of hypothalamo-hypophyseal function is uncertain. The occasional accompaniment of this condition by macrogenitosomia[15] or Fröhlich's syndrome,[16] as in the patient in Case 1, would suggest such a possibility. The relationship of the pituitary body to water retention and secretion has brought forth a suggestion by Marburg[17] that possibly this organ is implicated in the etiology of nonobstructive hydrocephalus.

The mode of the action of vitamin E in aiding in absorption of tissue exudates still remains unknown. Pappenheimer, Goettsch, and Jungherr[18] have succeeded in producing encephalomalacia with hydrops of tissues of body in chicks on an E-deficient diet. Administration of vitamin E produced reversal of symptoms in affected birds. Dam[19] has also found that deficiency of vitamin E affects the capillary system directly so that it is unable to withstand the normal osmotic pressure of the blood, and this increased permeability is made more evident when there is an increase in cholesterol, or sodium chloride, or phosphates in the blood. Besides, he was able to produce similar improvement in capillary permeability of experimental chicks on an E-deficient diet by lipocaic injection, instead of vitamin E, which would suggest that the action of vitamin E is possibly nonspecific as far as its influence on capillary permeability is concerned. I have also observed increased absorption of tissue exudate in selected patients with muscular dystrophy[20] and in patients with arthritis deformans[21] while these patients were receiving wheat germ oil. This would again suggest a probable nonspecific effect of vitamin E.

The existence of a maternal deficiency of vitamin E during the latter period of pregnancy, thus acting as direct cause of the hydrocephalus, should also be considered. Pappenheimer and his associates[18] have previously demonstrated that vitamin E deficiency produces different pathologic changes in various species of animals. It is probable that the response to vitamin E therapy is greater in children than in adults, the reaction to its administration differs in the female from the male,[21] and in the pregnant female the amount required varies with the state of pregnancy. This would help to explain, if it can actually be proved that lack of sufficient vitamin E in the pregnant mother is responsible for some cases of congenital hydrocephalus, why resorption of the fetus takes place in some instances in mothers on an E-deficient diet, while in others the effects of the deficiency are manifested in hydrocephalus, myatonia,[22] or muscular dystrophy in the newborn infant.[20]

The relationship of hydrocephalus to spina bifida has never been fully determined. It is probable that in some cases the hydrocephalus existed before birth, and the excessive accumulation of fluid in the subarachnoid spaces of brain and spinal cord prevented complete closure of the neural tube. The meningocele sac after birth also acts as an accessory absorptive membrane,[23] and the surgical removal of the sac

thus results in the development of the hydrocephalus. The improvement observed in patients with meningocele and hydrocephalus following administration of vitamin E would suggest a possible connection between vitamin E deficiency in the mother and disturbance of water secretion-absorption mechanism in both conditions. (The fact, however, that administration of a certain vitamin or combination of vitamins produces favorable results does not in itself imply that a deficiency of these vitamins existed in the body. The action of certain vitamins, when given in doses beyond the physiologic needs, is actually that of a drug with specific therapeutic potentialities. This would aid in explaining the varied beneficial responses reported with vitamin therapy in divergent pathologic states where no vitamin deficiency could be demonstrated.)

The general improvement observed in the treated patients as manifested by increase in alertness, improvement in muscle tone and muscle strength, and reduction of nystagmus is probably also partly due to the neurotropic and myotropic factors present in wheat germ oil. There is no doubt, however, that the mechanical removal of the excess fluid from the tissues exerted a salutary effect on the patient's general condition. This relief from excessive hydration, especially in the case of the optic nerves, would help explain the appearance of a response to visual stimuli which was previously absent. It is probable that the excessive fluid accumulation within the nerve sheaths produced constriction of the optic nerves in the optic foramina with resultant optic atrophy.

No indication was found for the use of larger doses than 1 to 4 c.c. of wheat germ oil daily, the actual amount depending on the age of the child and response to therapy. It is also probable that some of the unfavorable results reported with vitamin E therapy were partly due to the Gargantuan doses administered. Vitamin B complex was found in the past[20] to enhance the effectiveness of vitamin E and for this purpose was used as a vehicle for the wheat germ oil.

This investigation opens up a fruitful field for the study of the results from vitamin E administration in cases of cretinism and myxedema, and also in Ménière's syndrome and migraine in the female, where intracellular edema is a possible additional etiologic factor in selected cases; also in premenstrual tension states where improvement has frequently resulted following reduction of fluid and salt intake or following administration of ammonium chloride.[24] Early experimental results in several patients with such conditions have proved successful. It also would be worthy of an experimental trial in cases of nutritional edema, nephrosis, and other instances where disturbance of fluid metabolism exists.

SUMMARY AND CONCLUSIONS

Vitamin E in the form of wheat germ oil has been administered to nine children with congenital, nonobstructive hydrocephalus. Four of the children had noncomplicated hydrocephalus; five had hydrocephalus

accompanied with meningoceles of various sizes. Two of the children with meningoceles were operated on while receiving the medication.

In all the treated patients arrest or marked slowing down of progression of hydrocephalus occurred. There was reduction in nystagmoid movements of eyes, improvement in visual acuity, increase in mental alertness, concomitant improvement in muscle tone and strength. In the cases operated on for removal of meningocele, satisfactory postoperative healing took place and no hydrocephalus developed, although bulging of fontanels was present before the operation.

Disappearance of spinal fluid rhinorrhea, complete healing of a broken down meningomyelocele sac, with arrest of hydrocephalus and absorption of subcutaneous exudate of lower extremities, took place in a case of hydrocephalus associated with an extensive meningomyelocele and Fröhlich's syndrome.

In three patients with cases of hydrocephalus with optic atrophy where little or no response to visual stimuli was observed before treatment was begun, the children, after several months of treatment, were able to distinguish objects held in front of them as manifested by their reaching out correctly for these objects.

It is suggested from this study that nonobstructive hydrocephalus is produced in certain cases by a congenital disturbance of the hematoencephalic barrier. Vitamin E apparently has a regulating effect on capillary permeability and thus aids in adjustment of the spinal fluid secretion absorption mechanism. Whether a vitamin E deficiency in the mother is the cause of the congenital hydrocephalus or the salutary effect is nonspecific in nature and is due to the action of vitamin E directly on the capillary cell membranes or the blood constituents or indirectly through the pituitary is yet to be determined.

The probable nonspecific effect of vitamin E on tissue exudates in such divergent conditions as arthritis deformans and fibromyositis, in selected cases of muscular dystrophy, and in cases of cretinism and hydrocephalus would suggest one common denominator in these conditions; namely, excessive hydration of tissues caused by changes in cellular permeability, with vitamin E apparently as an efficient regulator of this disturbance. Its use in cases of nephrosis, nutritional edema, and other cases of edema of unknown etiology would also deserve a therapeutic trial.

The results obtained with vitamin E would suggest, also, the advisability of placing every infant with progressive hydrocephalus on vitamins E and B therapy before subjecting the child to surgery.

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CHEMICAL AND ENZYMIC STUDIES OF THE DUODENAL CONTENTS OF INFANTS

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SOMEONE has said that only about 50 per cent of "preliminary reports" were ever followed by the final paper. However, these studies of the duodenal contents of eleven infants are the follow-up of the preliminary report published seventeen years ago on the duodenal analyses of twenty-five infants.[1] One of these infants was suffering from acute diarrhea when first examined but convalescent one month later (Tables I and II), one had sprue, and nine were convalescent from various diseases (Tables III and IV).

METHODS

Collection.—Specimens of duodenal contents were obtained one-half to ten hours after a meal by the method previously described.[1] Three of the infants (8, 9, and 10) also were fed while the duodenal tube was in situ. In addition to the duodenal tube, with the exception of Patients 2 and 3 (the first two specimens of the latter), another tube was kept in the stomach to drain away the gastric contents in order to lessen the contamination of the duodenal contents. To detect gastric contamination the last five patients were given water containing a few drops of phenolphthalein every half hour. Phenolphthalein at the pH of the duodenal contents is colorless and does not interfere with the colorimetric pH determination, yet even 0.2 c.c. of this phenolphthalein containing water could be detected in a 5 c.c. aliquot of the duodenal contents by adding 0.1 normal sodium hydroxide to it. All specimens contaminated with gastric contents were discarded, except in experiments after feeding.

Specific gravity in some specimens was determined by weighing 5 c.c. portions and in others, by a pyknometer calibrated to 1 mg. accuracy.

Surface tension (S. T.) was determined by a stalagmometer, the tip of which satisfied the requirement that the ratio of the radius of the tip to the cubic root of the volume of the drops formed should be between 0.95 and 0.76. Taking the surface tension of water as 1.00, the results were expressed as relative to water according to the formula:

$$\text{S. T.} = \frac{\text{Specific gravity of duodenal fluid} \times \text{number of drops of water}}{\text{Number of drops of duodenal fluid}}$$

As the surface tension of water is about 73 dynes, the figures multiplied by seventy-three were the absolute values. The drop method was used because it gave the dynamic instead of the static force as determined

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TABLE I

PATIENT'S DATA DURING AND AFTER DIARRHEA

PATIENT	DATE	AGE (MO.)	WEIGHT (POUNDS)	CONDITION	DIET	TIME OF LAST FEEDING	TIME OF TUBE INTRODUCTION	TIME OF SPECIMEN COLLECTION	SPECIMEN NUMBER AND HOURS AFTER LAST MEAL	AMOUNT OF DUODENAL CONTENTS OBTAINED
1	Nov. 4, 1926	5½	12 13/16	Acute diarrhea and otitis media; three watery stools daily; temp., 102 to 103° F.; flat weight curve	Protein Milk	8 A.M.	12 noon	1 to 2 P.M.	I (5 hr.)	Not measured
								2 to 3 P.M.	II (6 hr.)	Not measured
1	Dec. 3, 1926	6½	13 12/16	Convalescent; diarrrhea and otitis media; one formed stool daily; temp., 99 to 102° F.; weight increasing	Whole milk and farina	6 A.M.	11:15 A.M.	12:10 to 1:30 P.M.	I (6 hr.)	14.5 c.c.
								1:30 to 2:00 P.M.	II (7 hr.)	5 c.c. (Contained phthalein)
								2:00 to 4:10 P.M.	III (8 hr.)	2.5 c.c.

TABLE II

RELATION OF THE RESULTS OF DUODENAL ANALYSES TO THE STATE OF DIGESTION

PATIENT	DATE OF SPECIMEN	SPECIMEN NUMBER AND HOURS AFTER LAST MEAL	SPECIFIC GRAVITY	SURFACE TENSION RELATIVE TO WATER	TRYPSIN UNITS (AVERAGE PER C.C. OF DUODENAL CONTENTS)	AMYLASE UNITS (AVERAGE PER C.C. OF DUODENAL CONTENTS)
(During Acute Diarrhea)						
1	Nov. 4, 1926	I (5 hr.)	1.005	0.467	4	219
		II (6 hr.)	1.005	0.456	5 (4.5 av.)	150 (184 av.)
(One Month Later, After Recovery of Normal Digestion)						
1	Dec. 3, 1926	I (6 hr.)	1.001 (?)	0.467	86	429
		II (7 hr.)			102	795
		III (8 hr.)			72 (87 av.)	633 (619 av.)

TABLE III

PATIENTS' DATA; TEN INFANTS WITH NORMAL DIGESTION

PATIENT	DATE	AGE	WEIGHT (POUNDS)	CONDITION	DIET	TIME OF LAST FEEDING	TIME OF TUBE INTRODUCTION	TIME OF SPECIMEN COLLECTION	SPECIMEN NUMBER AND HOURS AFTER LAST MEAL	AMOUNT OF DUODENAL CONTENTS OBTAINED (C.C.)
2	Oct. 7, 1926	3 yr.	23 15/16	Sprue	Whole lactic acid milk and junket	6 A.M.	10 A.M.	11 A.M. to 12:08 P.M.	I (5 hr.)	
								12:08 to 1:47 P.M.	II (6 to 7 hr.)	
								1:47 to 2:48 P.M.	III (8 hr.)	
3	Oct. 15, 1926	5 mo.	11 7/16	Convalescent; diarrhea and otitis media; temp., 101° F.; no diarrhea; flat weight curve	Whole lactic acid milk and farina	6 A.M. (No water by mouth)	10:15 A.M.	11:35 A.M. to 12:30 P.M.	I (6 hr.)	15.5
								12:30 to 12:55 P.M.	II (7 hr.)	13.
								1:30 to 2:30 P.M.	III (8 hr.)	5.5
								2:30 to 3:30 P.M.	IV (9 hr.)	5.5
4	Oct. 20, 1926	8 mo.	19 13/16	Convalescent; strangulated inguinal hernia; no diarrhea; temp. 99° F.	Whole sweet milk and farina	6 A.M. (No water by mouth)	10:30 A.M.	11:45 A.M. to 12:15 P.M.	I (6 hr.)	10.3
								12:15 to 1:10 P.M.	II (7 hr.)	15.
								1:10 to 2:10 P.M.	III (8 hr.)	4.
								2:10 to 3:10 P.M.	IV (9 hr.)	8.
								3:10 to 3:45 P.M.	V (10 hr.)	11.
5	Oct. 29, 1926	7½ mo.	12 6/16	Convalescent; diarrhea and otitis media; temp., 98° F.; no diarrhea; flat weight curve	Whole lactic acid milk and farina	6 A.M. (No water by mouth)	10:30 A.M.	11:15 A.M. to 12 Noon	I (5 hr.)	7.3
								12 Noon to 1 P.M.	II (6 hr.)	8.
								1:00 to 2:10 P.M.	III (7 hr.)	5.5
6	Nov. 10, 1926	7 mo.		Preoperative bilateral reducible inguinal hernia; no diarrhea; temp., 99° F.		6 A.M.	10:15 A.M.	12:30 to 1 P.M.	I (7 hr.)	15. Other specimens contaminated with gastric contents

7	Nov. 22, 1926	9 mo.	13 1/16	Convalescent; dysentery and otitis media; six soft but not watery stools daily; temp., 98° F.; flat weight curve	Whole lactic acid milk	6 A.M.	10:30 A.M.	11:15 A.M. to 1:15 P.M. 1:15 to 3:05 P.M. 3:05 to 4 P.M.	I (5 to 6 hr.) II (7 to 8 hr.) III (9 hr.)	10.5 8.5 6.5
8	Dec. 15, 1926	13 mo.	20 1/16	Convalescent; pneumonia and otitis media; two to three semifluid stools daily; temp., 99° F.; flat weight curve	Whole sweet milk and egg	6 A.M. and 5 P.M.	11 A.M.	11 A.M. to 3:25 P.M. 3:25 to 4:25 P.M. (Fed at 5 P.M.) 5 to 5:15 P.M. 5:15 to 5:45 P.M. 5:45 to 6:15 P.M. 6:15 to 8 P.M. 8 to 8:20 P.M.	I (5 to 8 hr.) II (9 hr.) III (During feeding IV (½ hr.) V (1 hr.) VI (2 hr.) VII (3 hr.)	 15 6 15 (Mixed with food) 15 (Mixed with food)
9	Dec. 21, 1926	20 mo.	23 15/16	Convalescent; U. R. I. and mediastinal tbc.; no diarrhea; temp., 99° F.; flat weight curve	Whole sweet milk and vegetables	6 A.M. and 3:35 P.M.	12:50 A.M.	12:50 to 3 P.M. (Fed at 3:35 P.M.) 3:50 to 3:55 P.M. 3:55 to 4:20 P.M. 4:20 to 4:45 P.M. 4:45 to 5 P.M.	I (7 to 9 hr.) II (During feeding) III (½ hr.) IV (1 hr.) V (1½ hr.)	16
10	Dec. 28, 1926	14 mo.	13 1/16	Convalescent; pneumonia and otitis media; no diarrhea; temp., 99° F.; weight increasing	Whole sweet milk	6 A.M. and 3 P.M.	11 A.M.	11:30 A.M. to 1:05 P.M. 1:05 to 2:55 P.M. (Fed at 3 P.M.) 3 to 3:15 P.M. 3:15 to 4:15 P.M. 4:15 to 5:15 P.M.	I (6 hr.) II (7 to 9 hr.) III (During feeding) IV (1 hr.) V (2 hr.)	14.5 12 4
11	Jan. 5, 1927	25 mo.	29 8/16	Convalescent; pneumonia and epituberculosis; no diarrhea temp., 100 °F.	Child diet	7 A.M.	1:15 P.M.	1:45 to 3:30 P.M.	I (7 hr.)	7

TABLE IV

CHEMICAL AND ENZYMIC DETERMINATIONS OF DOUDENAL CONTENTS; TEN INFANTS WITH NORMAL DIGESTION

PATIENT	DATE OF SPECIMEN	SPECIMEN NUMBER AND HOURS AFTER LAST MEAL	SPECIFIC GRAVITY	SURFACE TENSION RELATIVE TO WATER	BILE ACIDS (MG. %)	pH	TRYPSIN UNITS (AVERAGE PER C.C. OF DUODENAL CONTENTS)	AMYLASE UNITS (AVERAGE PER C.C. OF DUODENAL CONTENTS)	RATE OF FLOW OF DUODENAL CONTENTS (C.C. PER HOUR)
2	Oct. 7, 1926	I (5 hr.)					63	5090	
		II (6 to 7 hr.)					63	4875	
		III (8 hr.)					63 (63 av.)	6165 (5377 av.)	
3	Oct. 15, 1926	I (6 hr.)	1.017	0.556			141	224	17‡
		II (7 hr.)	1.003		*		77	332	31‡
		III (8 hr.)			*		99	262	5.5
		IV (9 hr.)			*		99 (104 av.)	313 (283 av.)	5.5 (14.7 av.)
4	Oct. 20, 1926	I (6 hr.)	1.004	0.462			91	158	20.6
		II (7 hr.)	1.005	0.459			61	161	16
		III (8 hr.)	1.006	0.462			90	166	4
		IV (9 hr.)					52	180	8
		V (10 hr.)					52 (69 av.)	92 (151 av.)	18.6 (13.4 av.)
5	Oct. 29, 1926	I (5 hr.)	1.006	0.445	150		266	614	9.6
		II (6 hr.)	1.007	0.456	146		32	649	8
		III (7 hr.)	1.008	0.456	333		60 (119 av.)	649 (637 av.)	4.7 (7.4 av.)
6	Nov. 10, 1926	I (7 hr.)	1.007	0.460	133.3	6.9	60 (60 av.)	56 (56 av.)	30

7	Nov. 22, 1926	I (5 tc 6 hr.)	1.009	0.484	166.6	7.0	?	?	5.2
		II (7 to 8 hr.)	1.010	0.484	116	8.0	?	?	4.6
		III (9 hr.)	1.010	0.476	208	8.2	?	?	7.2 (5.6 av.)
8	Dec. 15, 1926	I (5 to 8 hr.)		0.455		6.9	61	576	Contaminated
		II (9 hr.)	1.004	0.434		6.8	199	699	15§
		III (0 hr.)	1.002	0.571		6.8	116 (125 av.)	840 (705 av.)	24
		IV (½ hr.)		0.480		5.4	?	?	Contaminated
		V (1 hr.)		0.552		5.4	?	?	Contaminated
		VI (2 hr.)					?	?	Contaminated
		VII (3 hr.)		0.599			?	?	Contaminated
9	Dec. 21, 1926	I (7 to 9 hr.)	1.006	0.436		7.9	106	2764	7.4§
		II (0 hr.)		0.435		6.1	66	328	Contaminated
		III (½ hr.)		0.477		5.8	126	397	Contaminated
		IV (1 hr.)		0.445		5.6	135	502	Contaminated
		V (1½ hr.)				5.6	372 (161 av.)	1029 (1004 av.)	Contaminated (7.4 av.)
10	Dec. 28, 1926	I (6 hr.)	1.004	0.458		8.2	162	717	9§
		II (7 to 9 hr.)	1.006	0.448		7.8	241	1256	6.5§
		III (0 hr.)	1.005	0.464		7.0	144	1917	16
		IV (1 hr.)		0.473		5.4	167	721	Contaminated
		V (2 hr.)		0.423		5.2	230 (189 av.)	224 (967 av.)	Contaminated (10.5 av.)
11	Jan. 5, 1927	I (7 hr.)	1.007	0.475			320 (320 av.)	2949 (2949 av.)	4
Mean values			1.006	0.459	150	7.8†	99 (134 av.)	595 (1348 av.)	8.0 (11.6 av.)

*No acetone or volatile fatty acids were found.
†Five to ten hours after a meal; the mean value within two hours of a meal was pH 5.6.
‡No stomach tube used for these specimens.
§Before feeding.

by the ring method. In vivo the intestinal contents are in constant agitation, and it seemed unlikely that an undisturbed surface would be formed at the interface of the intestinal wall and duodenal contents. By this method the surface tension of breast milk was 0.635 (relative to water); whole lactic acid milk, 0.596; pasteurized whole sweet milk, 0.627 to 0.636; and absolute alcohol, 0.244 to 0.246.

Bile acids were estimated by Raue's method.[2]

Hydrogen-ion concentrations were estimated colorimetrically.

Trypsin values were obtained by the viscosity method of Northrop and Hussey,[3] using 3 per cent gelatin at pH 7.4 as the substrate. A unit is the amount of enzyme which requires sixty minutes to reduce the initial viscosity of the gelatin 20 per cent. Although this viscometric technique is more accurate than most of the other enzyme methods, parallel determinations rarely give the same result,[4] and so averages of several titrations have been used.

Amylase was determined by the same viscosity method, using 2.5 per cent starch suspension at pH 7.0 as the substrate[5]; the units were calculated similarly to those of trypsin.

RESULTS

The specific gravity of fasting duodenal contents, as shown in Table IV, was low (mean, 1.006; extreme, 1.002 to 1.010), except in the first sample of the patient in Case 3 (1.017) which probably was contaminated with gastric juice and therefore discarded. These results are in agreement with those of Rehfuss[6] in normal adults, who found variations between 1.002 and 1.008.

Surface Tension.—Brinkman and Szent-Györgyi[7] demonstrated that surface-active substances, sodium glycocholate among others, altered the permeability of collodion membranes. This suggested that bile salts and other surface-active substances present in the duodenal juice may influence the intestinal absorption. On the other hand the digestive enzymes are of colloidal nature, and adsorption of the surface-active substances on their particles may influence their activities by changes in the electrical charges. As shown in Table IV, the surface tension of the duodenal contents of fasting infants was fairly constant (mean, 0.459; extremes, 0.434 to 0.484). The surface tension of the duodenal contents of the infant with diarrhea (patient 1, Table II) was within the variations of the other infants. In spite of the fact that bile salts are undoubtedly the main source of surface-active substances in duodenal contents, the surface activity was independent of variations in the concentration of bile acids (Patients 5, 6, and 7); even an increase of more than 200 per cent in the third sample of Patient 5 caused no change in surface tension. Although the surface tension of mixtures of fatty acids, bile salts, and other surface-active substances varies with the hydrogen-ion concentration, pH changes in the upper parts of the small intestines did not significantly change the surface tension of the

duodenal contents. In Patient 7 (samples I and II), the surface tension remained the same although the pH increased from 7.0 to 8.0, and in Patient 9 (samples I and II) the surface tension remained constant although the pH decreased from 7.9 to 6.1. Even such great variations in pH as 8.2 and 5.4 in samples I and IV of Patient 10 caused little change in surface tension (0.458 to 0.473). If the trypsin activity may be taken as an index of the amount of pancreatic secretion in the duodenal fluid, there was no correlation between changes in the surface tension and the relative amount of pancreatic juice in the duodenal contents. Centrifugation of duodenal juice at high speed did not alter the surface tension. After standing in a refrigerator for four days the duodenal contents became cloudy and their surface tension increased from 0.462 to 0.497 and from 0.459 to 0.512, respectively; that is, the surface activity diminished, indicating that some of the surface-active substances were precipitated. These surface-active substances are adsorbed completely on charcoal at neutral reaction as was demonstrated by shaking two specimens with charcoal for ten minutes; the supernates became water clear and their surface tension was 1.0; that is, that of distilled water. Although dilution should decrease the concentration of surface-active substances, the fivefold dilution of a sample of duodenal juice decreased the surface tension from 0.467 to 0.448; that is, the surface activity increased. This was in agreement with Goiffon's observation,[8] that the tenfold dilution of a bile sample decreased the surface tension from 40 to 32.5 dynes. The incubation of 2 c.c. portions of a sample of duodenal juice for one hour and fifteen minutes with an equal amount of pasteurized whole (sweet) cow's milk, followed by the addition of 2 c.c. of water, caused the surface tension to decrease from 0.467 to 0.423; that is, the surface activity increased. When the same sample was similarly incubated with whole lactic acid milk, the surface tension rose to 0.472. This difference was surprising because the dilution of samples of duodenal contents produced a lowering of the surface tension, and whole lactic acid milk itself had a lower surface tension than that of sweet milk (0.596 and 0.627, respectively). The probable explanation for the difference in the effect of sweet and lactic acid milk is that addition of lactic acid milk probably lowered the pH below 6.0; Verzár and Kúthy[9] found that the surface tension of a glycocholate fatty acid mixture fell when the pH was lowered from 8.5 or 7.5 to 6.25, because near the neutral zone a soluble complex of fatty acid-bile salt was formed, which had a very low surface tension, but if the hydrogen-ion concentration were further reduced, this complex separated and the fatty acid precipitated out and the surface tension rose again. After feeding sweet milk formulas to three infants, the surface tension of the chyme was definitely higher in one (Patient 8), but in the other two (Patients 9 and 10) the surface tension had only a minimal rise as compared with the fasting state. Even in Patient 8 the tendency to maintain the surface tension of duodenal contents in a narrow

range was recognizable. These observations suggest the presence in the body of a complicated buffer mechanism regulating surface tension, which might be partially explained by the following facts: (a) The surface tension of an equal mixture of sodium glycocholate and sodium taurocholate is higher; that is, the surface activity is less than that of a similar concentration of either salt alone, and thus they counteract each other;[10] (b) a similar antagonism exists between lecithin cholesterol with respect to surface tension; (c) the addition of protein to glycocholate solutions influences their surface tension;[11] (d) the surface tension of bile increases on the addition of small amounts of serum (protein), although the serum itself decreases the surface tension of water;[8] (e) changes in pH alter the surface tension;[9] (f) the paradoxical effect of dilution of the duodenal contents on the surface tension is similar to the effect of dilution on the surface tension of serum.

Hydrogen-ion Concentration.—Within two hours of a meal, the mean duodenal pH was 5.6 (extremes, 5.2 to 7.0). This acidity probably was due to the admixture of, or the stimulation by, gastric contents, as the mean pH during the fasting state (five to nine hours after a meal) was 7.8 (extremes, 6.8 to 8.2). Schiff and co-workers[12] found in nine healthy infants a pH variation of 6.8 to 7.6; Dienst and Doering[13] reported pH 7.0 to 7.8 in adults. Both these authors drained the stomach contents away by a second tube, as was our technique. Myers and co-workers[14] found a mean duodenal pH of 7.0 in adults. Hume[15] observed pH variations of 6.66 to 7.64 in a young adult with a posttraumatic duodenal fistula. Imes[16] found the isolated duodenum of dogs to have a hydrogen-ion concentration of from 7.0 to 7.88. The lower figures usually reported in the literature possibly were due to failure to prevent contamination with gastric juice. A hydrogen-ion concentration of 7.0 is the optimal reaction for the duodenal amylase of children[17] and adults.[14]

Enzymes.—The mean trypsin value was 99 units per cubic centimeter (extremes, 32 to 372), and the mean amylase units, 595 per cubic centimeter (extremes, 56 to 6,165). There was no apparent relationship between the time after meals and the number of enzyme units per cubic centimeter of duodenal fluid. No explanation could be found for the low amylase value (56 units per cubic centimeter) of Patient 6. As shown in Table II, there was a marked diminution in trypsin and amylase secretion during diarrhea. Perhaps this lack of duodenal enzymes and the attendant accumulation and fermentation of undigested and unabsorbed food in the duodenum may have been responsible for the diarrhea.[1]

The rate of the formation of duodenal fluid during fasting, as judged by the flow from the tube, varied from 4 to 31 c.c. per hour (mean, 8.0 c.c.). These variations occurred in the same individuals on the same day from hour to hour. Cycles of more or less abundant formation of duodenal fluid were observed in the majority of the patients. In the

individual case it may have been due either to increased pancreatic or duodenal mucosa secretion or to an increased flow of bile. The data in Table IV make it unlikely that the variation in the flow of duodenal contents was due to admixture of gastric contents, except in Patient 3 whose first sample of duodenal juice had a specific gravity and a surface tension out of the range of the other samples, and who did not have an additional stomach tube in situ. In this patient the rate of duodenal fluid formation decreased from 31 to 5.5 c.c. per hour in samples II and III when the stomach tube was introduced. In Patient 4 the constancy of the specific gravity and surface tension of the duodenal contents indicated that contamination with gastric contents probably was not the explanation for the variation between 4 and 20.6 c.c. per hour. In samples I and III of this patient the pancreatic enzymes were of the same concentration in spite of a fivefold variation in flow, suggesting that a change in the flow of bile or duodenal mucosa secretion was not significantly different from the change in the pancreatic secretion. In samples I and II of Patient 5 the rate of the fluid formation, the bile acid concentration, and the amylase strength remained practically constant, while the trypsin activity markedly decreased; in sample III the volume decreased but the strength of the bile acids increased much more than the trypsin activity, indicating that the bile flow was less diminished in this period than was the pancreatic secretion. In Patient 10 the constancy of the surface tension and specific gravity, the high pH, and especially the absence of phenolphthalein in the juice excluded the possibility of gastric contamination as the cause of the variation in samples I, II, and III. In this patient the enzyme activity varied inversely with the flow in samples I and II. These great variations in the duodenal juice formation have been commented on by other investigators.[12, 15] During the first ten to fifteen minutes after the feeding of milk formulas (with phenolphthalein added to it), a significant increase in the duodenal flow was observed in Patients 8 and 10. As alkalization of the samples failed to indicate the presence of phenolphthalein, the increased duodenal flow probably was not due to the admixture with the fluid food from the stomach, especially as the pH did not change at all in Patient 8 and diminished only slightly in Patient 10. It might have been due to reflex stimulation by the act of feeding. In Patients 8, 9, and 10, when the presence of food appeared in the duodenal contents, the amounts of duodenal fluid were not reported, as obviously they were much altered by the amounts of food in them. These measurements of the rate of formation of duodenal fluid would have been more accurate if the specimens had been collected by a Miller-Abbott tube, the balloon of which is distal to the duodenal bucket and prevents the escape of duodenal contents into the jejunum. The possibility of gastric juice contamination would have been reduced by Abbott's procedure of attaching a second balloon one or two inches

above the duodenal bucket and inflating it when the bucket is passed into the duodenum so that it becomes impacted in the pylorus.[18]

SUMMARY

The mean values for the specific gravity, surface tension, bile acids, pH, trypsin, amylase, and the rate of flow of the duodenal contents of nine infants with normal digestion, one suffering from sprue and one from diarrhea, are presented. The diarrheal patient had had a marked reduction of duodenal trypsin and amylase. In the others the surface tension of the duodenal contents was stable in spite of variations in the rate of flow and the concentration of enzymes and bile acids.

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IDIOSYNCRASY TO METALLIC MERCURY, WITH SPECIAL REFERENCE TO AMALGAM FILLINGS IN THE TEETH

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IDIOSYNCRASY to mercury may give rise to many curious clinical pictures. In sensitive persons the application to the skin of ointments containing small amounts of mercury may result in various eruptions (urticaria, erythema, edema, bleb formation); fever, at times hyperpyrexia; prostration and unconsciousness.[1] I reported a number of cases of idiosyncrasy to ammoniated mercury in children in 1941.[1] One of the cases described by me concerned a girl aged 15 years who, after having had ammoniated mercury ointment applied to her scalp by a hairdresser, developed a severe generalized urticaria and edema twenty-four hours later. A year later a small amount of the same ointment was inadvertently applied to an abrasion. Although the ointment was removed almost immediately, a generalized severe reaction followed. Her third attack occurred without an ointment having been applied. The interesting information obtained was that the day before the appearance of symptoms she had attended a class in physics and had handled a glass funnel through which another student had poured metallic mercury. The funnel was handed her without having been washed. Apparently enough mercury had adhered to the glass to cause symptoms when transferred to the girl's hands.

This was my first encounter with symptoms of idiosyncrasy due to metallic mercury. Several months after this girl's case had been reported she went to a dentist who put an amalgam filling in one of her teeth. The following day her lips were swollen, and an erythematous eruption appeared on the skin about her mouth and on her cheeks. It was realized that the eruption was probably due to mercury, but since it seemed likely that the lesions were due to local application of bits of amalgam on the dentist's fingers while filling the teeth rather than to absorption from the amalgam already in the tooth, it was decided to leave the fillings in place and await the results. Within two days the eruption cleared up and the girl remained well.

Cases of idiosyncrasy have been described after the application to the skin of unguentum hydrargyri, Almkvist mentioning urticaria after its application for pediculosis.[2] This ointment contains from 30 to 50 per cent of metallic mercury, which is supposedly present in the form of minute particles,[3] so that here, too, we have symptoms following the application of metallic mercury. That this metal may cause severe local cutaneous lesions is illustrated by the following observation:

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CASE 1.—A boy aged 10 years was seen because of an eruption which his mother thought might be one of the exanthemas. He had been kept at home because of a cold and, except for the coryza, did not appear ill. However, on the morning of the day on which I saw the child he developed an eruption over the lower abdomen, the thighs, and the genitals. The skin over this area was deep bluish red, hot, and thickened. The border of the eruption was quite definitely marked as in erysipelas. The skin of the penis and scrotum was edematous. There were no other symptoms. There was no fever. The boy seemed to feel well and complained only of slight itching. The peculiar color of the eruption, its urticarial nature, and the absence of other symptoms pointed toward a local contact dermatitis. The boy was questioned about ammoniated mercury ointment but none had been used. However, when the boy heard the word "mercury," he informed us that he had been constructing a barometer, that the metallic mercury had spilled on the carpet, and that he had sat on the floor in his open pajamas scooping up the mercury to replace it in the apparatus. The metal had apparently come in direct contact with the areas of skin involved by the eruption. His differential blood count showed 8 per cent eosinophiles. He recovered in three days without any treatment.

CASE 2.—K. M. an American school girl aged 14 years, first seen March 12, 1942, complained of a generalized eruption accompanied by severe itching of ten days' duration. She is an only child. The family history was negative except for the fact that for one year the father had severe urticaria, the cause of which was never discovered. The patient was born at term and her infancy and childhood were quite normal. She had had chicken pox and measles but had otherwise been well. At the age of 4 years she was given a dose of calomel, following which she developed a generalized eruption which lasted two days. During her attack of varicella she was given a blue medicated soap following the use of which she broke out into "hives." At the age of 7 years an ointment containing yellow oxide of mercury was applied to the eyelids, following which there was marked swelling and edema of the lids and circumocular regions lasting several days. At the age of 12 and again at 13 years a dentist filled a tooth with amalgam following which she developed circumoral swelling and red blotchy eruption on the lips and cheeks. This persisted for a week and then disappeared.

Three weeks before the onset of the present complaint she again went to the dentist who filled two teeth with "silver" fillings (amalgam). Some orthodontic work, consisting of soldering on a platinum and gold band, had also been done. About a week after this, large welts appeared on the child's body and the itching became intense. Sleep was greatly disturbed, appetite was lost, and the girl was unable to continue at school. Many remedies had been tried, none with any success. The mother brought the child to me and suggested that the mercury fillings in the teeth might be the cause of the symptoms. There was no history of the ingestion of any new or unusual foods. No new soap or cosmetics of any kind had been used. There had been no contact with any new or unusual substance such as new underwear or mattress or pillow. No new furs had been worn. There was no history of recent contact with any animal.

Physical examination revealed a normal girl except for the condition of the skin. Her weight was 120½ pounds; her height, 59 inches. Her trunk and extremities were covered with giant urticarial swellings, some of them as large as the palm of the hand. The child kept scratching continually. Mucous membranes were normal, as were the eyes, ears, heart, lungs, lymph nodes, and abdominal viscera. The urine was normal. There was no anemia. The white cell count was 11,700. The differential count showed 65 per cent adult polymorphonuclear cells, 2 per cent juvenile forms, 1 per cent large lymphocytes, 32 per cent small lymphocytes.

The mouth appeared normal. There was no inflammation or redness of the gums near the filled teeth nor where the platinum band came in contact with the soft tissues.

Because of the history of previous evidence of sensitiveness to mercury brought on by calomel, yellow oxide ointment, a "blue" soap (probably containing bichloride of mercury), and the amalgam fillings a year before, it seemed plausible that the mother was right and that the amalgam fillings were at fault. On my advice the dentist was asked to remove the fillings. One was removed on March 12. This was followed by a real exacerbation of the symptoms, including a temperature rise to 102° F. The legs and feet became so swollen that shoes could not be worn. On March 14 the second amalgam filling, and with it the platinum band, was removed. Within twenty-four hours the symptoms subsided and the child remained perfectly well.

A specimen of the child's blood was obtained and a passive transfer test performed. When a small amount of ammoniated mercury ointment was applied to the prepared site, a definite red wheal appeared. A control application on the opposite unprepared arm was completely negative.

A sample of the material used as a band on the teeth, a combination of platinum and gold, was examined for mercury, but none was found present.

COMMENT

The case of this patient is then one of sensitiveness to mercury not only in a number of its chemical combinations but also to the substance in the metallic state. In sensitive persons minute amounts of amalgam may come in contact with the lips and face during the dental operation and cause eruptions lasting for several days after the dental work has been done. This occurred once in the case of the girl first referred to in this paper and twice in the patient in Case 2. In the patient in Case 2 the third time a tooth was filled with amalgam an incubation period of ten days occurred before symptoms appeared. Moreover the eruption this time did not spontaneously disappear after a few days but persisted for two weeks in the form of giant urticaria until both the offending fillings had been removed. It was of interest to note that the removal of one filling caused a temporary severe exacerbation of symptoms with fever. It was only when the second filling and the band were removed that the symptoms at once subsided. What relationship the band around the tooth had to these symptoms I am unable to say. It is possible that the band affected the gum in such a manner that absorption of the metal took place more easily.

Mercury poisoning due to amalgam fillings was first noted by Fleischmann.[4] Later much work was done on the subject by Stock.[5] As a result of his publication a special clinic was established for the study of the effect of amalgam on the general health. His researches in this field are summed up in a comprehensive article published in 1936.[6] Stock believes that much of the symptomatology is due to the inhalation of air which contains mercury emanating from the fillings. He warns of danger of this inhalation during the removal of fillings and cites cases where the act of removing the amalgam caused exacerbation of the symptoms as in the case described in this communication. Excavation

of the fillings should be accompanied by suction to prevent the inhalation of minute particles of amalgam. Although most of Stock's work deals with mercurial poisoning, he also mentions that in susceptible persons symptoms of idiosyncrasy to mercury may make their appearance.

A case very similar to my Case 2 was described by Blumenthal and Jaffe in 1929.[7] A woman, aged 30 years, showed an eruption on her face on three different occasions immediately after a tooth had been filled with amalgam. After a fourth filling the mucous membranes of the nose and throat and the skin of the face, neck, and shoulders were the sites of a severe dermatitis. The authors proved hypersensitiveness in the patient by passive transfer tests.

Recently Sweet[8] briefly referred to this subject and showed by radiographs that excess of amalgam is often left in the gums after teeth have been filled. He warned against this as a possible cause of toxic symptoms later on.

Although cases of idiosyncrasy to the mercury in amalgam fillings are referred to in the literature,[9] most of the articles are in German and many dentists and physicians do not seem to be acquainted with the subject. It therefore seemed worth while to call attention again to this interesting clinical picture.

SUMMARY

Three cases of idiosyncrasy to metallic mercury are described. All occurred in children and all showed symptoms referable to the skin. In two instances metallic mercury applied to the skin was the active agent. In two, amalgam fillings were the etiologic factor. In one of these, symptoms of severe urticaria continued until the removal of the fillings. This cause of urticaria may be more common than is ordinarily supposed.

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CONGENITAL PULMONARY CYSTS

Report of an Infant Treated by Lobectomy With Recovery

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SINCE the first recorded case of congenital cystic disease of the lung by Bartholinus in 1687, numerous articles on this subject have appeared in the literature. The many theories as to etiology, the varied nomenclature, and the controversy as to which cases are congenital or acquired has resulted in placing this subject in a state of marked confusion.

In the presentation of this case report, we feel that there cannot be any doubt as to the congenital origin of the condition in this infant. The clinical, roentgenographic, operative, and pathologic findings would place this case in the group of "expansile balloon cysts" with a one way valve mechanism at the orifice, communicating with a bronchus (using the classification of Anspach and Wolman[1]).

The patient (M. F.), a female infant, was born Sept. 30, 1941, at full term of a primiparous mother by normal delivery and weighed 5 pounds, 12 ounces at birth. Both the father and mother are living and well, and there is no history of any congenital abnormalities in the family.

Although no gross abnormalities were noted at birth, the mother recalls that the infant seemed to breathe with difficulty almost since birth. In spite of this fact she thrived well on breast feeding, weighing 6 pounds, 12 ounces upon discharge from the hospital in two weeks.

Two weeks later, or when the infant was 1 month of age, she was first seen by one of us (C. C. F.) because of failure to gain any weight during this period. Upon examination at this time marked dyspnea was noticed, the chest being partially fixed in expansion with marked infrasternal and suprasternal tugging. Percussion revealed hyper-resonance over the entire right chest and the upper portion of the left chest. The heart was found to be markedly displaced toward the left mid-axillary line with the point of maximal impulse located in the fourth interspace. Auscultation confirmed this cardiac displacement and also revealed the presence of a few crepitant râles in the right chest, posteriorly, with no impairment of resonance in that area.

The child was immediately hospitalized, and fluoroscopy the same afternoon confirmed the marked mediastinal shift but failed to reveal any fluid levels in that area. A roentgenogram revealed the presence of three air-containing cysts in the upper and middle thirds of the right chest anterior to the cardiac shadow (Figs. 1 and 2).

As the dyspnea seemed progressive, an attempt was made to give relief by inserting a No. 20 gauge needle on a 50 c.c. syringe into the cystic area, as indicated by the roentgenogram, in the right anterior axillary line. The positive pressure within the cyst immediately displaced the plunger of the syringe to about the 40

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Presented before the Philadlephia Pediatric Society, March 10, 1942.

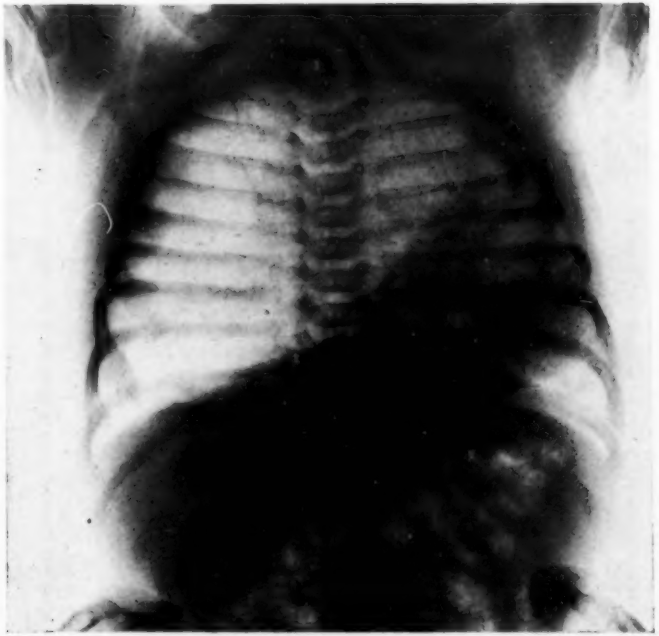

Fig. 1.

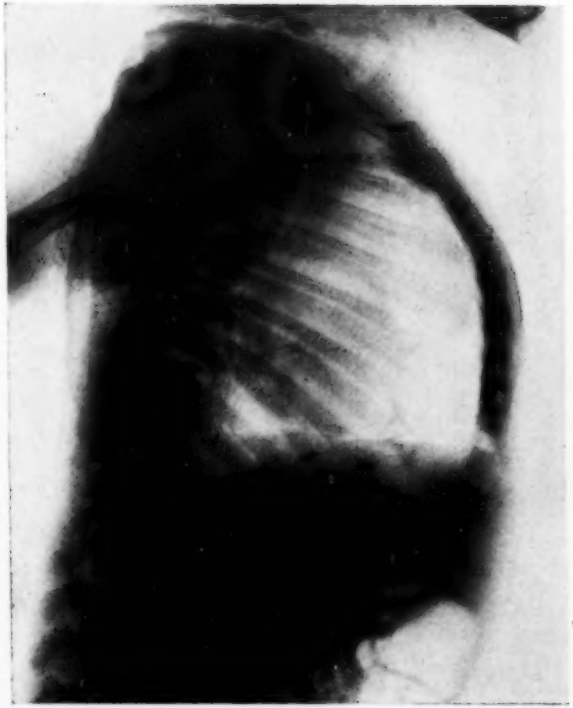

Fig. 2.

Fig. 1.—Roentgenogram on admission showing large air-containing cysts in right middle and upper lobes pushing cardiac shadow to left chest wall.
Fig. 2.—Lateral view on admission.

c.c. mark, and a similar result was obtained when the needle was reinserted about three interspaces below. This procedure was followed by a moderate relief of the dyspnea and a slight shift of the mediastinum to the left.

By the next afternoon the dyspnea had become progressively worse, and there was also some noticeable subcutaneous emphysema in the right chest wall extending up slightly above the clavicle.

One of us (C. P. B.) recommended operative intervention, and that same evening the operation was performed by two of us (C. P. B. and F. T.).

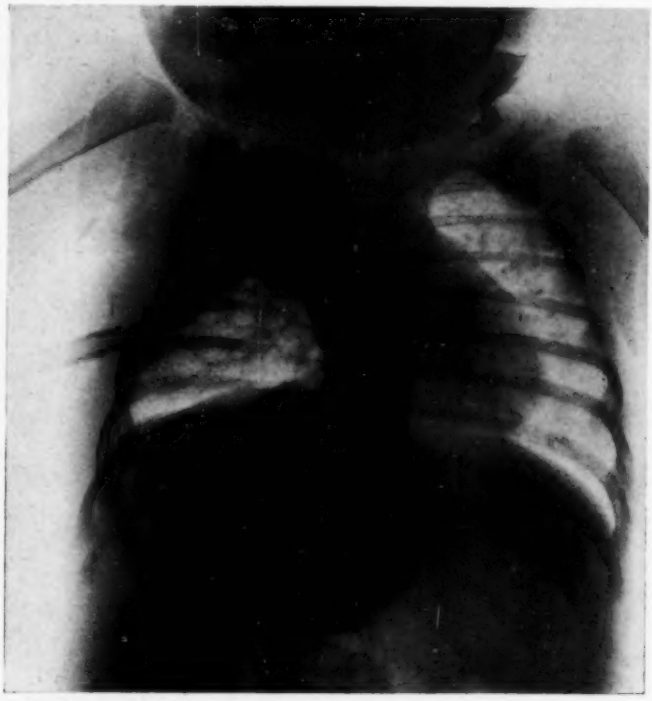

Fig. 3.—Second postoperative day, showing return of cardiac shadow to a near normal position and drainage catheter in area of right upper lobe.

Operative Technique.—Under local anesthesia an incision was made in the fifth interspace from the midscapular to the anterior axillary lines. The incision was carried through the intercostal muscles and pleura, and wide retraction of the ribs was easily accomplished with a self-retaining retractor. Cystic lung immediately protruded through the wound, and examination revealed multiple cysts of the right upper and middle lobes. A tourniquet was placed around the hilus of the upper and middle lobes and the lobes amputated with a formalin knife. The hilar stump was secured witih a whip-over silk suture and the tourniquet removed. Closed drainage, using a No. 14 catheter, was established after a layer closure of the wound.

Postoperative Management.—A blood transfusion of 100 c.c. followed by a continuous venoclysis of 5 per cent glucose in saline and distilled water (10 to 15 drops per minute) was given. The infant was placed in an oxygen tent and twelve hours postoperatively was satisfactorily taking food by mouth, at which time the con-

tinuous administration of parenteral fluids was stopped. Sulfathiazole was administered orally for seventy-two hours as a prophylaxis against pleural space infection. The drainage catheter was removed on the fifth postoperative day, at which time roentgenograms showed a return of the mediastinum and heart shadows to a near normal position (see Fig. 3). The infant's progress was uneventful, the wound healing by primary intention. The patient was discharged on Nov. 20, 1941, in excellent condition.

Pathologic Report (Dr. H. Russell Fisher).—There was a specimen consisting of a lobe of lung tissue 7.5 by 5.5 by 2 cm. in size which previously was opened. It contained a large cystic cavity and several smaller cavities located just beneath the pleural surface and occupied a considerable portion of the lobe. All cavities had a thin translucent wall and contained only air; the large cavity was subdivided by thin trabeculae.

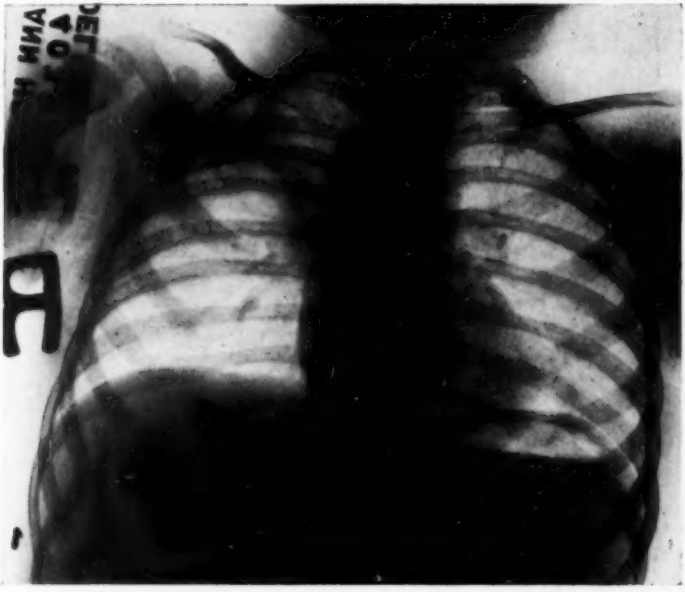

Fig. 4.—Roentgenogram one year after operation, showing little abnormality save for the small area of density at the root of the amputated lobes.

Microscopic examination showed that bronchiolar structures formed the cavity walls, which were made up of a mucosa bearing columnar epithelium superimposed upon a hyperplastic muscularis. Other sections from the lung tissue showed generalized dilatation of the bronchioles down to their respiratory portions, associated with a hyperplasis of the bronchiolar musculature. Air sacs and alveoli were uninvolved. There was no evidence of inflammatory reaction. The diagnosis was cystic disease of the lung.

Subsequent Clinical Course.—At 12 weeks of age the child weighed 12 pounds, 8½ ounces, and her physical examination revealed no abnormalities. By the time she was 1 year old she weighed 21 pounds and 2 ounces and was 30½ inches long and appeared normal in every respect. Her roentgenogram (see Fig. 4) confirms this impression, although there is some evidence of continued organization of the area from which the lung was removed. To date this has produced no clinical

symptoms or physical signs, and it is to be hoped that complete resolution will gradually follow.

DISCUSSION

We have been unable, by a close study of the literature, to find any reported cases of lobectomy with recovery in so young a patient, probably because the operation may not have often been attempted at this age. It is our hope that this report may stimulate further operative investigation into these hitherto fatal cases. Sauerbruch,[2] who performed fifty-eight lobectomies for congenital bronchiectasis with six deaths and fifty-one complete cures without a fistula, stated his conviction that the treatment of choice for a congenital malformation is extirpation of the involved lobe. He feels that congenital cystic disease is not a rare clinical entity, although it is little appreciated by pediatricians. Schenck[3] feels that the surgical extirpation of the cystic defect, or lobectomy, is the only rational form of treatment in selected cases.

The relative simplicity and ease of performance of this operative procedure in infants should be stressed. The absence of adhesions, the smooth outline of the hilus, and the small structures liken them very much unto those of experimental animals such as the cat. In many communities where trained thoracic surgeons are not available, we feel certain that if this procedure were investigated by the general surgeons, many infants could be successfully operated and cured of a congenital lesion that is often fatal.

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STREAMLINED INFANT FEEDING

A Feeding Routine Utilizing Earlier Addition of Solid Foods and Fewer Feedings

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THIS report is based on a study of a group of infants, with the object of showing that most young infants reaching the age of about 6 months can be placed on a schedule of three meals a day. This is desirable and advantageous and can be instituted with excellent results. The many practical advantages (and absence of disadvantages) are sufficient evidence to prove that this method of infant feeding is superior to that still advocated in the standard pediatric textbooks. We have used this method of feeding for the past twelve years in approximately 3,000 infants.

The patients in this study were those seen in an average private pediatric and infant-feeding practice. The infants were breast and bottle fed, full term, and premature. They were examined at least once each month during the first year of life. The efficacy of this method of infant feeding is based primarily upon the infant's own tolerance for the diet. In other words, if the infant is in good health, growing normally in height and weight, has a good appetite, no digestive disturbances, sleeps well and is happy, then this particular diet schedule is advisable. The infant is the sole judge of the amount of food he requires. The number of ounces of formula at each feeding is left up to the baby so that he receives as much as he desires or needs.

Experience with this method of feeding has shown that a majority of infants can tolerate a diet schedule of three and four feedings in twenty-four hours early in infancy. If the baby receives more and richer food at a feeding, then it is not necessary to feed him so often. The rate of growth and development of the infant is the chief criterion as to the amount and number of feedings he will require. The age of the infant is of minor importance. The individual development of each infant is the deciding factor as to when to begin solid food. Solid foods are added to the diet when the infants have reached the following approximate weights (these weights are purely arbitrary but fit in well with this procedure):

10 pounds	Banana, applesauce
10 to 12 pounds	Cereals
12 to 14 pounds	Vegetables and soups
12 to 16 pounds	Fruits
16 to 18 pounds	Meat, fish, cottage cheese

Hard foods such as toast and bones are added at 5 to 6 months. This is dependent upon the motor ability of the infant to hold and manipulate

foods. All food is mashed with a fork at about 6 months, whether the infant has teeth or not. Whole fresh pasteurized milk is usually advised when the infant weighs about 16 pounds or over.

For the purpose of this study, 100 consecutive cases were taken from our records as we felt that this number would adequately represent other hundreds on this same schedule during the past twelve years. Of this number, twenty-two of the infants had been breast fed for periods ranging from one to six months. Nine had been born prematurely. The average birth weight was 7.23 pounds (Table I). The average age when four feedings were instituted was 3.1 months, and the average weight at this time was 12.78 pounds. The average age when three feedings were started was 5.75 months, and the average weight was 18 pounds. The average weight at 1 year of age was 23.41 pounds and the average length was 30 inches. All of the resulting figures listed are within the average normal range for the infants of this particular age group.

TABLE I

ANALYSIS OF 100 CASES

Average birth weight for 100 infants	7.23	pounds
Average four feedings—age	3.1	months
Average four feedings—weight	12.78	pounds
Average three feedings—age	5.75	months
Average three feedings—weight	18	pounds
Average weight at 1 year	23.41	pounds
Average height at 1 year	30	inches

In order to determine whether this method of feeding had any detrimental effects upon the infants, the following factors were considered with each infant: Upper respiratory infections, anorexia, vomiting, diarrhea, and skin eruptions. Table II lists the results of these observations. No upper respiratory infections occurred among forty-three infants. The average number of infections for the entire group was less than one. This incidence may be considered as good, or better, than that ordinarily observed among infants.

TABLE II

MINOR SYMPTOMS OCCURRING DURING THE FIRST YEAR (100 CASES)

	NUMBER OF CASES
Upper respiratory infections	80
Anorexia	2
Vomiting (several other minor cases)	1
Diarrhea (simple type and easily controlled)	8
Skin eruptions (attributed to food)	9

With regard to anorexia, *only two cases occurred.* This is unusual considering the high percentage of anorexia cases in the infants which receive more frequent feedings. In fact, with this type of feeding where the infant is the chief judge of his own diet, anorexia is less apt to occur. *This is one of the main reasons for advocating fewer feedings.* In all

animal life, appetite is created by hunger. An infant will eat a larger total amount when the intervals between feedings are longer, in the same manner as any other individual. The baby with anorexia is rarely found among those fed on this routine.

There was only one bad case of vomiting which started when the infant was 3½ months of age and persisted until the age of 8 months, after which it ceased. This was due to a pylorospasm. There were several minor cases of vomiting of short duration which were easily controlled. These were usually due to the onset of an infection or a mild gastrointestinal disturbance. Overeating did not occur. Infants will stop eating when satisfied.

Diarrhea occurred in eight infants but was of the simple type, lasting only a few days. Constipation was rare and was easily controlled by adding more fruit or vegetable prepared in coarser fashion. Of the total number of infants studied, nine developed skin eruptions that were attributed to food. Eight of these infants had eczema and one had urticaria.

DISCUSSION

Tables I and II show that young infants between the ages of 3 and 6 months can tolerate very well fewer feedings than are ordinarily suggested. At each feeding the infants are fed all the food they desire. When they are placed on four feedings daily, no food is given from 6:00 P.M. to 6:00 A.M.

The indications for putting a baby on four feedings daily are:

1. When the weight approaches 10 to 12 pounds, or if the infant is 3 to 4 months old, but weighs less than 12 pounds.
2. Start solid foods earlier when the supply of breast milk is insufficient.
3. If the baby has to be awakened for his 10 P.M. feeding.
4. If large amounts of strong formula are taken at a feeding (no more than 8 ounces are fed at a time) solid food is then added.
5. When cereal is started in his diet (about 10 to 12 pounds).
6. If rapidly growing baby requires more food than usual.

The infant on four feedings daily is on the following approximate schedule:

6:00 A.M.	Milk
10:00 A.M.	Cereal, milk
2:00 P.M.	Banana or apple, milk
6:00 P.M.	Cereal, milk

The formula consisted of fresh or evaporated milk with the addition of water and plain table sugar. Approximately 2 ounces of fresh milk per pound was used. The fresh milk seldom exceeded 24 ounces daily; the evaporated milk never more than 1 large can (13 ounces) and the sugar averaged 3 large tablespoons (1½ ounces) per formula. We suggest any of the whole grain cereals cooked with equal parts of milk

and water in a single boiler for fifteen minutes. Precooked cereals are very satisfactory. The cereals are fed at 10 A.M. and 6 P.M. and the infant is allowed as much as he desires. Raw ripe banana is readily tolerated and practically all babies like it. The mother is instructed to feed more solid foods and less milk. When solid foods are added to the diet it is not necessary for the infant to take as much milk. A pint daily is usually a good average.

The fruit and vegetables added to the diet are usually those available for the other members of the family. All the common vegetables and fruits are advised unless the infant manifests some idiosynerasy to any of them. These are prepared as for the rest of the family and are sieved or mashed when the infant is able to tolerate them. Canned infant foods are also desirable during the first few months. In allergic infants new foods are added at a later age, starting with smaller amounts and longer intervals between each new food.

The three-meal-a-day schedule of feedings should be instituted on the following indications:

1. When the infant weighs about 17 to 18 pounds, or is 5 to 6 months of age but weighs less than 17 pounds.
2. When the appetite lags, especially for the 2 P.M. feeding.
3. When the infant sleeps past his 6 A.M. feeding and is gaining well.
4. Small stature babies that do not require large amounts of food.
5. When the infant is receiving a variety of solid foods, cereal, soup, vegetable, and fruit in addition to milk.

When the infant is on three meals daily, the following schedule is used:

7:00 to 8:00 A.M.	Fruit or juice, cereal, toast, bacon, milk
12:00 NOON	Soup or vegetable (any kind, mashed) prepared the same as for the rest of the family Meat: ground beef, broiled liver, or chicken or Fish, salmon, halibut, tuna Dessert: fruits, gelatine Milk
3:00 P.M.	Fruit juice, toast, bones (only if infant is hungry and eats other meals well)
6:00 P.M.	Soup, vegetables or cottage cheese, fruit, and milk.

All foods are mashed or chopped. Toast, zwieback, and bones are given to the infant as soon as he is able to hold and chew them. The infant on a schedule of three meals daily gets whole fresh pasteurized milk, undiluted with water or carbohydrates. We discontinue sterilization of bottles, nipples, etc., at about 4 months of age when the baby begins to put his hands and other objects in his mouth.

Orange juice was usually given at about 1 month of age. We found that where an allergy existed, raw ripe banana was usually well tolerated and served the purpose very well. No synthetic vitamin C preparations

were necessary. No clinical cases of scurvy or vitamin C deficiency were found.

Vitamin D preparations consisting of either fish oil concentrates or viosterol were used routinely in doses averaging from 5 to 10 drops daily. There were no cases of clinical rickets and very few that required larger doses. Because of the early addition of various foods, the infant receives more natural vitamins in his food and requires less of the synthetic vitamin preparations.

Our observations show definitely that infants on this routine have better teeth and smaller and less infection of the tonsils and adenoids than control groups. A critical survey of these findings will be published later.

CONCLUSION

A consecutive group of 100 infant feeding cases selected from about 3,000 infants over a twelve-year period was analyzed. The advantages of early addition of solid foods, fewer feedings, and longer intervals are as follows:

1. The elimination of many feeding problems, particularly anorexia.
2. Fewer dietary changes are necessary.
3. The infant is just another member of the family and is made to fit into the family routine. It is easier to give three or four feedings than five or six.
4. Solid and varied foods are given earlier.
5. The feeding schedule is more natural or physiologic, since the infant is the chief judge of the amount of food he wishes to eat.
6. There are fewer cases of rickets and nutritional diseases. Less vitamins C and D, as given to the infants in cod-liver oil and orange juice, are needed because of the natural vitamins in his food.
7. Many mothers remark about how easy it is to raise their babies. There is nothing that has to be specially prepared for the infant when he is put on three meals daily at 17 to 18 pounds, or when he is about 6 months of age. There is more rest and less work for the mother.

The rationale of this routine has been proved by the fact that these babies have all developed into happy, normal infants with practically no feeding problems.

1155 10TH AVE., NORTH

The Pediatrician and the War

Processed Baby Foods

At the meeting of the Executive Board held in June, action was taken in regard to the limitation of processed baby foods to children under 18 months of age. The following letter has been received from the Office of Price Administration.

Gentlemen:

Your letter of June 10, 1942, addressed to Mr. Austin C. Hoffman, Food Price Division Director, has been referred to this office for reply.

We are in accord with your thinking concerning processed baby foods with the exception of restricting the sale of processed baby foods to infants under 18 months of age. While it may be administratively possible to amend Ration Order 13 in such a manner as to accomplish your recommendation, it is felt that this move would mean placing the burden of administration in the hands of the retail grocery operators who, as you know, are already overburdened with work. It is felt that they, the retail grocers, are not in a position to handle this additional job.

We would like to point out that since March 1, 1943, beginning date of the processed foods rationing program, we have done a number of things that we think will help protect processed baby food supplies. To begin with, dehydrated soups were reduced to a very low point value and eventually removed from rationing altogether, and now canned soups, juices and other more or less stapled processed foods have been brought down to the point price range of processed baby foods. As stated above, we feel that this action will take quite a bit of pressure (adult buying for adult consumption) off of processed baby food.

Available supplies of baby foods have been determined and a certain per cent of this availability has been scheduled to move by periods (monthly). During March, 1943, we had scheduled to move 616,000 standard cases; actual movement during March was 250,000 cases. We had scheduled to move during April 679,000 cases; the actual movement was 439,000 cases. We have only preliminary figures for May; these show the actual movement during the month substantially smaller than the amount scheduled to move during the month.

Of the total availability of processed baby food, vegetable base represents forty per cent; fruit base, twenty-seven per cent; meat compound base, twenty-seven per cent; and dessert base, six per cent. To date the movement of the different varieties has been in line with or below this schedule of movement which, of course, is based on supply.

We appreciate letters such as yours; it has merit, and it has been given its due consideration by this office. If in the future it is deemed advisable that our control of processed baby foods should be changed, your recommendation will be given further consideration at that time.

Lead Pellets in Evaporated Milk

Due to the tin conservation program it has been necessary to use a solder with a very low tin content in soldering the cans containing milk for marketing. At excessive temperatures such solder may cause lead and tin pellets to drop into the cans. Laboratory research has proved that these lead and tin pellets are not injurious to health under ordinary circumstances. The use of the nipple on the infant feeding bottle will naturally filter out any such pellets which might by chance have gotten into the formula. Hence from the practical standpoint there is little or no danger of an infant swallowing such pellets. The chief difficulty seems to be the anxiety of the mother upon finding such pellets.

In the Army it has been recommended, because of an occasional finding of such pellets, that all evaporated milk be strained from the can to the food being prepared. The pellets will ordinarily be small but not small enough to pass through an ordinary kitchen sieve. When evaporated milk is used for infants or older children drinking from the cup or is used in cooking, it may be of value to carry out this precaution.

THE EDITORS.

American Academy of Pediatrics

Proceedings

TWELFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., NOV. 4-7, 1942

Panel Discussion on Allergy and Immunotherapy

Chairman: Bret Ratner, M.D., New York, N. Y.

Associates: Warfield T. Longcope, M.D., Professor of Medicine, Johns Hopkins Medical School, Baltimore, Md.

Paul R. Cannon, M.D., Professor of Pathology, University of Chicago Medical School, Chicago, Ill.

Harry L. Alexander, M.D., Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

John A. Bigler, M.D., Highland Park, Ill.

CHAIRMAN RATNER.—The title of this panel discussion may, at first hand, seem somewhat obscure, for we are wont to think of allergy in relation to foods, pollens, animal emanations, and so on rather than to immunotherapeutic agents. Yet the discovery of allergy and anaphylaxis at the dawn of the twentieth century was not concerned with the former antigens. Richet discovered anaphylaxis curiously enough through the use of a powerful primary poison, *actinocongestin;* and Pirquet and Schick unfolded the panorama of allergy from the sequellae ensuing from the use of the beneficent therapeutic agents, diphtheria antitoxin and antiscarlatinal serum.

Serum allergy in the human subject presents the counterpart of animal anaphylaxis. It is, of course, an unplanned experiment in the human species; yet every time a serum is injected the allergic phenomenon may develop. Light is cast on the immunologic concept of the antigen-antibody mechanism as it occurs in man under circumstances similar to controlled experimental conditions in the lower animal. Reactions and symptomatology are not limited to any single organ but may be manifest throughout the body, revealing the physiologic pathology and enlightening us as to the basis for our clinical observations.

Present-day immunotherapy includes the use not only of antisera and toxoids, but also of blood transfusions, blood substitutes, and sulfonamides. Because these materials have become so integral a part of immunotherapy, this discussion will deal expressly with the allergies resulting from their use. An intimate understanding of the whys and wherefores governing the choice of agents, dosage, preventive measures, and a recognition of the futility of certain practices should lead to the prevention of allergic catastrophies.

As profound a respect as I have for the scientific achievements of the age in which we are living, and I grant that specific advances have been made in the conquest of many diseases which in the past have been left to the mercy of nature,

yet I believe you will agree that our knowledge is still acquired largely through trial and error. The avalanche of therapeutic agents that stem from pharmaceutical houses overwhelms the unsuspecting physician who has no yardstick with which to measure the relative merits of respective preparations. Each proponent grinds his own axe and waxes warm in praise of his own product; nary a word is dropped that perhaps some other remedial agent or some other procedure may be better in a specific situation. Countless numbers of children have received antipneumococcal serum when only a select few needed it. Now countless thousands of patients are receiving sulfonamides when only a relatively small number need these phenomenal drugs; of course, I am thinking only in terms of civilian life. Some may say it is better to err on the side of safety and use these agents, even though not specifically indicated. It is my judgment, however, that those who practice the best type of medicine frown on such reasoning. We have passed through a period of wholesale tonsillectomies, wholesale mucous nasal resections, wholesale appendectomies, and so on ad nauseam. Let us pause now, lest we plunge headlong into an era of wholesale serum and sulfonamide therapy. Even at the risk of proving tiresome I would plead that we be circumspect, that we endeavor to separate the wheat from the chaff, and that we use judiciously the excellent remedial agents now available.

Perhaps it may not be amiss briefly to draw attention to the pivotal phase of allergy that may help to keep this complicated subject well in focus. Let us go back forty years to Charles Richet, the French physiologist, who made the following remarkable observation. He was experimenting upon dogs with an extract of certain sea fauna. He injected one particular dog, Neptune by name. This dog was unaffected by the first sublethal injection. Richet then went off on a holiday. Upon his return, some twenty-two days later, he again injected Neptune with the same extract. To his amazement, the dog rapidly went into shock, had a hemorrhage from the bowels, vomited copiously, and died within a few minutes. He had injected many animals prior to this, but never before had such a thing happened. He retraced his steps and came to the realization that he had fallen upon a heretofore unsuspected biologic phenomenon; *namely, that an animal that is injected with an otherwise harmless substance is changed somehow in his reaction to a subsequent injection of this same substance.*

The present war makes this subject a very timely one. Will our boys be made sensitive to some of the therapeutic agents being used so freely? Will sulfonamide allergy, for example, assume a prominent place after this war? Perhaps we may take solace in the thought that we are learning how to handle anaphylactic problems, and it is to be hoped that those who are spared from lethal war wounds will not be endangered through anaphylaxis.

Dr. Longcope, who, as you know, has contributed more to our understanding of the antigen-antibody mechanism of allergy than any other investigator in medicine or immunology, will open this discussion. Time will not permit him to tell us all he knows, but the nature of his observations are such that I am sure they will give us profound food for thought and a deeper insight into several pertinent questions in the field of allergy and immunotherapy.

Serum Sickness

Warfield T. Longcope, M.D., Baltimore

When I was asked to speak on serum disease at this conference it seemed to me at first that the subject was quite threadbare and there would be little new to say, but on further thought it became obvious that in the light of recent developments in the use of substitutes for human plasma and the wide employment

of the sulfonamides, serum disease and its related phenomena require reconsideration from a fresh point of view.

It must be recognized that our knowledge of this disease has been acquired almost exclusively from observations upon man and starts essentially with the classical work of von Pirquet and Schick in 1905. Although the condition had been recognized long before, it is justifiable to date the modern conception of the disease from their important monograph. Since then the publications upon serum disease and its related phenomena have been legion, and as the essential data have been collected in innumerable statistical articles, reviews, monographs, and textbooks, it is entirely unnecessary to reiterate them at this time. It is desirable, however, to point out that the statistical compilations are unavoidably based on results obtained from the use of whole blood serum or concentrated antisera of many varieties, employed for the treatment of different sorts of people, suffering from a number of diseases. It is thus apparent that these many variables impair the usefulness of statistics for any accurate analysis.

It is particularly important to keep this in mind in dealing with some of the components which go to produce serum disease, such as the antigen or sensitizing substance. The antigens employed so far, as compared with those studied in experimental anaphylaxis, make rather a short list. They consist largely of the proteins, which are present in serum from horses immunized to a variety of toxins and bacteria or of these antisera, concentrated and refined. The sera of other artificially immunized animals, such as rabbit, beef, sheep, and goat, have also been employed, but the vast majority of observations have been made after the use of horse serum, either for prophylactic or therapeutic purposes. It has long been known that the two predominating proteins in normal animal sera are a serum albumin and several forms of serum globulin, but the more exact physical methods of ultracentrifugalizing and electrophoresis in the Tiselius apparatus have shown that the composition of normal horse serum and human serum is characterized by the presence of albumin and three forms of globulin, known as alpha, beta, and gamma globulin. The albumin predominates while the gamma globulin is present in next largest amounts. Though the other protein fractions are present in much smaller amounts, this may not be commensurate with their importance. It has been found that the relative proportions of these various proteins are greatly altered in blood serum obtained from animals immunized to different bacteria and toxins, and there is a question as to whether new forms of protein may not make their appearance.

We must, therefore, recognize that administration of antitoxic and antibacterial sera, particularly when they are concentrated, may give rise to antibodies which differ from those produced by normal horse serum. It is now known that the different proteins of normal horse serum are specific in regard to their antigenic action. This was very beautifully demonstrated by Dale and Hartley many years ago when they showed that there were specific differences between the albumin and globulins of horse serum and that sensitiveness to euglobulin appeared several days before that to albumin. This, combined with the observations by Koch that beef serum was less likely to cause serum sickness than horse serum, has led recent investigators to study the antigenic property not only of beef plasma, but of purified serum albumin in hopes that it might be used as a substitute for transfusions with human plasma or serum. Taylor and Keys, using bovine serum, have confirmed Dale and Hartley's observations on horse serum. Further experiments by Taylor and his associates, by Eaton, and by Janeway and Beeson have shown that bovine albumin, even in comparatively pure state, is, however, antigenic and will occasionally cause serum disease when given intravenously in large quantities to human beings.

One might suppose that human serum was completely innocuous, but in rare instances, as has been shown by Dooley, serum disease may even follow injection of convalescent human serum.

Another important problem relates to the reaction following the injection of chemical substances. Illness closely resembling serum disease has been described as occurring almost regularly after the administration of nirvanol, used at one time for the treatment of chorea, while the so-called erythema of the ninth day occurs after the injection of many antisyphilitic arsenicals. It is now realized that there are reactions that follow the administration of most of the sulfonamide drugs which also simulate serum disease. It is not possible at this moment to discuss the fascinating subject of drug allergy, but reference must be made to the important researches of Landsteiner and his collaborators which have led to the demonstration that guinea pigs may be sensitized and made anaphylactic not only to the azoproteins, but when appropriate methods are used, also to certain pure chemical substances.

Mechanism of Serum Sickness.—Not only the quality and quantity of antigen bear upon the incidence of serum disease, but also the age, race, and constitution of the patient, together with his previous contact with the antigen. Thus children, in general, are more likely to have serum sickness than the aged, and Negroes are thought to be less susceptible than the white race, which Coca also found to be true of American Indians. Though the amount of antigen injected is important, still there are individuals in whom serum sickness appears after the administration of small amounts of antigen and others in whom the intravenous injection of enormous amounts of whole horse serum is not attended by the slightest evidence of serum disease. Roughly, however, the incidence of serum disease mounts with increasing quantities of serum or antigen administered.

Although anyone of these many variables may influence the incidence or occurrence of serum disease, not one controverts in any way the present conception of the immunologic basis for serum sickness and its related phenomenon. The original idea of von Pirquet and Schick was that the reaction resulted from a combination of antigen and antibody in the body. There is abundant evidence to show that this theory is correct and, further, that the combination takes place within or on the cell and not in the circulation. During its presence, however, antibodies are extruded into the circulation, and it has been shown by many experimenters that precipitins and anaphylactic antibody appear, that the Prausnitz-Küstner phenomenon can be obtained, and that the skin of the patients acquires sensitivity to the specific protein. Though these antibodies may appear during the course of serum sickness, they are usually found in the later stages or in convalescence, and their presence in the serum may well be considered as a result of the tissue reaction rather than the cause of the disease. It is nevertheless important to realize that with the appearance of these antibodies in high concentration in the serum, the antigen which was present during the early stages of the disease, disappears or diminishes, and that when serum disease does not result, humoral antibodies do not appear and the antigen remains in the circulation for weeks or months. In spite of this, however, the patient may eventually develop sensitivity to the specific protein. The conditions accompanying drug reactions are different inasmuch as it is difficult or impossible to demonstrate the presence of antibody in the serum and the skin of the patient rarely becomes sensitive to the particular chemical. That a variety of antibodies may appear in animals, however, under experimental conditions, has recently been demonstrated by Landsteiner.

Clinical Manifestations of Serum Disease.—The clinical manifestations of typical serum disease are so familiar that it is unnecessary to dwell upon them at length. There is a definite incubation period averaging from six to ten days or longer, and I need only remind you that the onset is usually abrupt and that the commonest

signs are eruptions, fever, edema, lymphadenopathy, and arthralgia. It is interesting to note that the eruptions are of various sorts—urticarial, erythematous, morbilliform, and erythema multiforme with occurrence occasionally of purpura. These rashes may recur and in a fairly definite sequence, urticaria being the first expression of the reaction and other forms of eruptions appearing later, so that it has been suggested that the different forms of eruption are dependent upon sensitization to the separate protein fractions of the serum. Single recurrence is observed in about 3 per cent of the cases, double recurrence or more in less than 0.5 per cent.

In rare instances the edema may affect the larynx, there may be cardiac irregularities or evidence of collapse, albuminuria with casts in the urine, and some reduction in the phenolsulfonphthalein output are not unusual. Both the central and peripheral nervous systems may be affected. Optic neuritis and choked disc may occur, and peripheral neuritis is not at all uncommon and frequently persists sometimes with paralysis for months. Leucocytosis may be marked during the early stages. Eosinophilia is not characteristic of the disease.

When the patient has previously received serum, the incubation period of serum sickness following a second injection is shortened to two or three days and the onset of symptoms may be fulminant, though the period of illness is comparatively short. This has been termed the accelerated reaction. In persons with extreme sensitivity, either natural or acquired, from a previous injection of serum, true acute anaphylactic shock and death may supervene. Kojis has collected accounts of sixty-one such deaths which he has carefully analyzed.

It is now interesting to consider the drug reactions in this connection. Though they simulate serum sickness, they differ somewhat in character. Nirvanol sickness, a well-defined disease, has an incubation period of from six to eight days and is characterized by fever and morbilliform, erythematous, and multiform eruptions with drowsiness and slight eosinophilia. Erythema of the ninth day following the first injection of the arsphenamines after an interval of seven to twenty days is a febrile exanthem which has recently been discussed and analyzed by Peters, who considers it similar to serum sickness. Toxic reactions to the sulfonamide group of drugs have been widely discussed and described. They are extremely varied and are probably dependent upon different causes. Symptoms such as nausea, vomiting, cyanosis, headache and the formation of renal calculi can be ascribed to direct toxic action of the drug or its acetylated form, but fever, eruptions, agranulocytosis, the optic neuritis which is occasionally seen, and probably hemolytic anemia may be due to a more or less specific sensitization phenomenon. Blake and Hageman have compared the febrile reactions and the dermatitis following the administration of sulfonamide to serum disease, and it has been shown that the second administration of sulfathiazole following some days after an original course of the drug may be followed immediately by a marked rise in temperature. One characteristic of these drug reactions is the accompanying eosinophilia.

Pathology.—Our information concerning the pathology of serum sickness, indeed of experimental anaphylaxis itself, is very imperfect. In the experimental animal reinjection of the specific protein into local regions, such as the subcutaneous tissue, the peritoneal cavity, and the joints, causes inflammatory reactions. Following repeated anaphylactic shocks disseminated foci of inflammation have been described in many organs. The Arthus phenomenon has been extensively studied by Opie, who found acute lesions in the blood vessels leading to intravascular thrombi with resulting necrosis. The observations upon the pathology of serum disease itself are extremely rare. Boots and Swift obtained an inflammatory exudate from the joints of a few patients with arthralgia. The fluid also contained horse serum. There are two important observations. The first was by Clark and Kaplan who had an opportunity to study the tissues from two patients who died

during serum disease following treatment with large doses of antipneumococcus horse serum. They found proliferative changes in the endocardium and in the intima of the large vessels and, in one case, a necrotizing arteritis and periarteritis of the smaller coronary arteries. Secondly, Rich has studied tissues from seven patients who were treated with antiserum and sulfonamides or with either one of these alone. In all of these patients the constant lesion, which appeared in the tissues, was an acute arteritis and periarteritis affecting the smaller blood vessels in a large variety of organs and presenting the pathologic picture of periarteritis nodosa. He concluded that vascular lesions of this type can be a manifestation of the anaphylactic type of hypersensitivity.

Diagnosis.—Diagnosis of serum disease is not difficult except under a few circumstances. Stiffness of the jaws, which may be the first symptom, results in great anxiety when it appears in an individual having had a prophylactic injection of tetanus antitoxin. Since urticaria is the only distinctive sign of serum disease, it may be extremely difficult without its presence to differentiate the onset of serum disease from the complications of pneumonia or of scarlet fever. When sulfonamide drugs are employed in combination with antisera, the situation is still further confused.

Prevention and Treatment.—Although concentration of antibodies and antitoxin in small amounts of serum reduces the bulk and is therefore a great step in advance, it does not obviate serum sickness. Many other methods have been employed in order to render the antiserum nonantigenic. Heat, acidification or alkalinization, peptic digestion, and treatment by taka diastase and other ferments have been employed, possibly with some degree of success. The most promising method, however, recently reported by Henry, is the effect of ultraviolet and visible light upon the antigenic property of normal horse serum. The method he employed rendered the serum so inert that it would theoretically require 100,000 c.c. of serum to produce the same sensitizing effect in guinea pigs as 1 c.c. of normal serum.

Pending further developments of methods to reduce or abolish the antigenic property of foreign serum, it still remains of the utmost importance to determine the sensitivity of the patient to a particular foreign serum before this serum is used for therapeutic purposes. Intracutaneous tests, conjunctival tests, and the intravenous test should all be performed with serum diluted 1:10 or 1:100, since whole serum is irritating. The intravenous test should be performed last; it is particularly important as it sometimes happens that the patient may not give a reaction either to the intracutaneous or the conjunctival test but may still be hypersensitive to the particular protein employed. Desensitization is difficult but may be successful if the patient is not too highly sensitized. Treatment of the disease is entirely empirical. Derrick, Hitchcock, and Swift thought that the arthralgia could be prevented or diminished in severity by continuous administration of salicylates or aspirin. These drugs, however, have no effect on the other symptoms. Subcutaneous injection of adrenalin will relieve temporarily the unbearable itching of the urticaria and is imperative in acute shock.

In conclusion, serum disease and the related phenomena must be regarded as an outward and visible sign of the processes of sensitization of the human being to a foreign protein and is accompanied and followed by the immunologic reactions which occur in experimental anaphylaxis in animals. A similar disease is observed after the administration of certain drugs. Efforts to obviate serum disease are being directed toward the use of a purified albumin fraction from bovine serum and attempts to render normal serum nonantigenic. So far, these experiments have not been completely successful. There is great danger in administering foreign proteins to patients who have acquired natural or artificial sensitivity to these specific proteins. Methods are available to detect such sensitization, and

therefore precaution should be taken to avoid these unfortunate accidents. Desensitization is difficult, and the treatment of serum disease is extremely unsatisfactory.

CHAIRMAN RATNER.—I was most desirous of having Dr. Cannon take up the question of the Arthus phenomenon, that allergic manifestation which is so bizarre in its necrotizing and destructive qualities that it would appear to belong to a totally different etiologic category. Its importance in human pathology is such that perhaps many pathologic conditions which are poorly classified at present may some day more correctly be attributed to this mechanism. Dr. Cannon's contributions to this field are so notable that it is a pity that we will not have the opportunity to hear him on this subject today. However, he has chosen a phase of immunology which perhaps is basically far more important than the Arthus phenomenon; namely, the "anamnestic reaction." You will learn from his remarks how vital a part this question of anamnestics plays in our everyday practice.

The term etymologically means "without amnesia"; that is, without the loss of memory. As the concepts underlying it are more generally understood, I am sure that this rather esoteric term will come to be used as commonly as allergy. In truth, allergy is "anamnesia". You have but to remember Richet's first experiment with the dog Neptune to realize that neither the dog's cells nor the fine mind of Richet had amnesia, for both recalled that a previous contact had taken place.

The Anamnestic Reaction

Paul R. Cannon, M.D., Chicago

The anamnestic reaction, in its narrowest sense, is the process whereby antibodies reappear in the blood as the result of a later nonspecific stimulation. For example, Conradi and Bieling, who gave the phenomenon its name, observed, in soldiers previously immunized against typhoid bacilli, the reappearance of specific antibodies for the typhoid bacillus during such infectious processes as miliary tuberculosis, malaria, typhus, pneumonia, Weil's disease, etc. They suggested the name "anamnestische serumreaktion" with the idea that the antibody-producing cells "remembered" their previous experience in forming antibody against the typhoid bacilli and were able to form the same type of antibody a second time under the influence of a heterologous stimulant. Bieling, Hektoen, and others thought of the process as essentially an allergic reaction. Interest in the phenomenon centered for many years on its practical importance in interfering with laboratory procedures, especially the Widal reaction, and comparatively little attention was given to its theoretic implications. I have discussed some of these implications elsewhere and will therefore restrict discussion to only a few aspects of the phenomenon here.

The anamnestic reaction may be elicited in many ways; one easy procedure is to inject a normal rabbit with a purified protein, such as swine albumin, and record the antibody curve until the antibodies have disappeared from the blood stream; a second injection of horse serum into this rabbit will engender not only antibodies specific for horse serum, but also antibodies specific for swine albumin. In other words, the second nonspecific stimulus reawakens the antibody-producing cells to fabricate antibody specific for the first antigenic stimulant.

The question of most interest in such a response is: What is the nature of the antibody-producing mechanism which makes such a process possible? The answer must be that a cell which has once metabolized antigen has been so altered that it retains the capacity to produce antibody long after the antibody has disappeared from the blood. This altered reactivity is independent, therefore, of several

antibodies and must reside in the cell itself. And inasmuch as recent evidence points conclusively to the fact that an antibody is a specifically modified molecule of globulin, any cell which forms globulin should, theoretically, be capable of becoming "sensitized" as the result of an antigenic stimulus and be able to react later anamnestically.

Although the intricate intracellular process of antibody production is still unknown, the most probable explanation is that an antibody is formed as the result of the intracellular synthesis of globulin under the influence of intracellular antigen. Antigenic molecules, acting as templates, influence the formation of globulin molecules which have a stereochemical relationship to the antigenic components present at the sites of formation of the antibody. Such an explanation furnishes an answer to the mysterious phenomenon of specificity. The specifically modified molecules of globulin are then cast off into the blood stream as antibodies, leaving the cell able to form additional ones so long as the antigenic templates remain within the cell. Another explanation is that, as the result of the entrance of antigenic molecules into an antibody-producing cell, new intracellular enzyme systems are generated which then persist. But regardless of the exact mechanism of antibody formation, the fact remains that such cells retain the potentiality to produce specific antibodies under suitable conditions of stimulation.

Confusion regarding the scope of the anamnestic reaction has resulted from a too rigid adherence to the idea that it results only from a nonspecific stimulus. There is no reason other than the historic one why this should be so. The accelerated response of antibody liberation after a second antigenic stimulation has been apparent ever since the experiments of Cole, in 1904, that a second immunization with typhoid bacilli will call forth an earlier and an intensified outpouring of specific antibodies against typhoid bacilli. Nevertheless, the term anamnestic reaction has been restricted too frequently to the nonspecific type of secondary response. In view of present-day information concerning the mechanism of antibody production, however, it would seem advisable to regard the anamnestic reaction as of two types, the nonspecific and the specific, both depending upon the same intracellular mechanism.

If antibodies are products of the intracellular synthesis of globulin, the antibody-producing cells throughout the body should be looked upon as a vast matrix from which antibody may come; and the liberation of antibodies into the blood is incidental to the more fundamental process of antibody synthesis. After antibodies disappear from the blood, the matrix remains, ready to start the process once more, when appropriately stimulated. Many features of tissue allergy and immunity can be more satisfactorily explained by such a mechanism, such as fixed drug reactions, local allergic phenomena, and regional variations in immunity.

From the practical point of view the anamnestic reaction enhances the rationale of nonspecific protein therapy, fever therapy, and the use of the so-called "booster" injections of antigens to elevate the antibody content of the blood after immunization with diphtheria and tetanus toxoids and other antigens. It may also explain why city dwellers previously exposed to various types of bacterial antigenic stimulants react, as a rule, more effectively to many kinds of infectious agents than do individuals from sparsely settled regions and who, consequently, have had fewer antigenic experiences capable of "tuning-up" the antibody matrix. It is possible, although not yet proved, that the heterophile phenomena, such as those observed in infectious mononucleosis or serum sickness, may be anamnestic reactions resulting from previous sensitizations to Forsmann antigen.

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CHAIRMAN RATNER.—Dr. Alexander's contributions in the field of allergy are many and fundamental. To him has fallen the lot of defining desensitization. That he has more fully understood the underlying principles of desensitization than many others is evidenced by the fact that he has successfully desensitized cases of severe serum hypersensitiveness, a problem more often marked by failure than success.

Desensitization is a moot subject. It embraces that phase of allergy which is more important from a practical standpoint than most others. It encompasses the issue of making allergic individuals more tolerant to the substances to which they are sensitive. It is closely related to immunity. An individual may be immune at one time and allergic at another, neither phase being static.

Desensitization

H. L. Alexander, M.D., St. Louis

The term desensitization is used clinically in a broad sense, since man does not become completely desensitized except for a brief period under unusual circumstances. With proper treatment, however, he will exhibit an increased tolerance to allergens which had previously caused him symptoms. When the term is used with this meaning, desensitization is but temporary and lasts a comparatively short time, as a rule, after treatment has been discontinued.

It is of significance that the mechanism of desensitization is imperfectly understood. As a matter of fact, evidence at hand indicates that no actual reduction of hypersensitiveness of the tissues occurs as the result of specific treatment. This is true at least for that type of allergy represented by the asthma-hay fever, or atopic, group of patients. For instance, the size of a skin reaction to a given allergen is frequently used as a measure of hypersensitiveness to that allergen. After specific desensitizing treatment with it, the skin reaction is usually not reduced in size, and the amount of circulating skin sensitizing antibody, atopic reagin, may actually be increased. However, specific treatment may result in marked clinical improvement.

There exists then, the following paradox: Treatment with a specific allergen to which a patient exhibits a marked hypersensitiveness may alleviate symptoms caused by that allergen and, at the same time, induce still more hypersensitiveness to it. To explain this phenomenon, there is evidence which indicates that parenteral treatment brings about relief of symptoms by the development of an antibody which neutralizes the antigen at fault. Since the antigen is thus bound to the neutralizing antibody, it is not available to react with its specific skin-sensitizing antibody in the blood or tissues, and thus clinical symptoms resulting from such contact are diminished.

The clinical importance of the imperfection of our knowledge of the mechanism involved in desensitization is reflected in the fact that this is no convenient measure of what one is accomplishing during treatment; neither is any information concerning it revealed except by eventual clinical results. For instance, given two individuals each with hay fever due to ragweed pollen, each with apparently similar degree of hypersensitiveness, and each receiving equivalent treatment, one may have a good clinical result and the other not. And yet, during treatment there has been no way of anticipating correctly what the ultimate effect will be. Very recently methods of measuring the neutralizing antibody formed during treatment have been devised, and these promise to reveal the degree of developing immunity.

Desensitization is applied clinically to patients with hay fever for the most part and is given prophylactically. It has particular usefulness in cases of marked hypersensitiveness to horse or other sera, where serum treatment is indicated. To give therapeutic serum under these circumstances is very dangerous. Programs of rapid desensitization, however, have been worked out, wherein a highly sensitized individual may be prepared to receive therapeutic sera in comparatively few hours.

Prophylactic injections are also of some apparent value not only in hay fever when they are given during the season, but also under other circumstances when the allergen at fault cannot be avoided, as with house dust or with occupational dusts. Although the mechanism of clinical relief may also be due to the development of a neutralizing antibody, this point has not been investigated.

Prophylactic desensitization by ingesting the allergen at fault has been used under various circumstances. Very small amounts of the offending food are taken by mouth according to given schedules and small increments are added daily. This method seems at least but partially successful, although, recently, good results have been recorded. There is substantial evidence of the absorption of food from the gastrointestinal canal into the systemic circulation so that there is reason to believe that antibodies may be formed when antigen is given in this manner.

In the past few years the oral route has been advocated for the administration of pollen antigen. Were this to be successful, it would of course be enormously advantageous. There has been a good deal of debate concerning the effectiveness of this procedure. The presence of antibodies in the blood stream as a result of pollen feeding has been claimed by some and denied by others. Clinical evaluation of any method used in the treatment of hay fever is always difficult because so many variables must be considered. It seems to be the consensus of opinion, however, that oral desensitization for hay fever is inferior to parenteral injection of pollen extract, and there has been a very limited acceptance of it.

There are other forms of allergy in which desensitization is used. One concerns contact dermatitis. Here, too, there has been controversy. Treatment by this means has been used for the most part in poison ivy dermatitis. Shelmire maintains that the amount of extract of *Rhus toxicodendron* required to reduce the hypersensitiveness of a severe case sufficiently to get good clinical results when given parenterally would be so great that its administration would be impossible. Other dermatologists share his point of view. On the other hand, there are numerous reports from reputable observers indicating that but a few parenteral injections of relatively small amounts have produced satisfactory clinical results in large numbers of patients. This discrepancy of opinion is due to the difficulty of establishing proper controls. It appears, however, that there may be a marked reduction of the patch test reaction which is a measure of hypersensitiveness and in clinical sensitivity by the use of the oleoresin and other extracts of *Rhus toxicodendron* given orally. By this route enormous doses may be taken over a long period of time. The effectiveness of treatment by parenteral desensitization of dermatitis caused by pollen oils or the many hundreds of other contactants is very questionable.

Inasmuch as no antibody has as yet been found to account for the hypersensitiveness of contact dermatitis, the mechanism through which improvement may occur during the process of apparent desensitization is wholly unknown.

Another form of allergy in which desensitization is of definite value is in eczematous dermatitis due to fungus hypersensitiveness. This is a relatively intractable disorder and not uncommon. Where positive skin reactions to very dilute extracts of trichophytin or oiidiomycin are positive, desensitization with these extracts given by intradermal injection may greatly improve such lesions.

One is dealing here with bacterial allergy, and again the reason for clinical improvement is not yet clear.

In physical allergy, especially in cases of urticaria in which hypersensitiveness to heat or cold exists (a rare condition), daily exposures to increasing temperatures carefully controlled may give dramatic results in a short time. An over production of histamine (H-substance) is thought to be responsible for symptoms, and desensitization apparently induces an antihistamine effect.

It has been the ambition of many to discover some way in which desensitization to all allergens could be effected with a single substance. The one most employed has been histamine. Theories explaining why histamine should be effective are, for the most part, confusing. It is presumed, although there is no proof, that injection of histamine will induce the elaboration of histaminase by the tissue cells; this in turn conteracts so-called H-substance which theoretically is the cause of allergic symptoms when antigen and antibody come in contact with each other. Despite gratifying reports of its effectiveness in asthma, hay fever, vasomotor rhinitis, and other expressions of allergy, our experience with it has been wholly disappointing.

Recently the administration of histamine linked to a protein has been used with the thought that true antibody formation could thus be stimulated. The final preparation is a histamine azoprotein. The protein employed is despeciated horse serum globulin. As yet, there has not been much clinical experience with this product, and although a few dramatic results have been reported, there also have been many complete failures. Until the method has been tried far more extensively, it cannot be thoroughly evaluated. Likewise, injections of acetylcholine as a universal desensitizing agent has had little support. The same holds true for giving peptone by mouth before meals in cases of food allergy.

In summary, it would appear that desensitization has a limited usefulness but, when indicated, especially in hay fever, may have great clinical value. The mechanism by which therapeutic results are obtained is evidently not by an actual reduction of hypersensitiveness or desensitization—at least, not in all cases—as is popularly believed. As indicated above, an immune process is developed by treatment wherein a neutralizing antibody is found which prevents the offending antigen from contacting sensitized tissue. Only in the past few years has this been revealed, and it is encouraging that an increasing number of investigators are being engaged with the problem of desensitization. In the near future the revelation of work now in progress in several laboratories may not only clarify much that is uncertain, but also may indicate a revision of our present clinical methods of treatment.

CHAIRMAN RATNER.—Dr. Bigler, it now devolves on you to present us with certain phases of the allergies resulting from the use of toxoids and vaccines, a problem which confronts us daily in our practice. It may be appropriate at this time to remark that apparently allergy is a broad subject. Richet was a physiologist, Pirquet a pediatrician, and on this panel are two internal medical men, a pathologist and two pediatricians. Pediatricians like Pirquet, Schick, Schloss, and others have pioneered in this field. It is my fond hope that a growing group of pediatricians will concern themselves with immunologic problems. With the child specialist lies the greatest burden, for it is he who sees the very beginnings of allergy, and it is he above all other practitioners who can do most in its amelioration and eradication.

Allergic Reactions Resulting From Toxoids

John A. Bigler, M.D., Chicago

Because of the increasing use of immunologic substances, there has been an awakened interest in the allergic symptoms or hypersensitiveness which these

matrials may produce. With the use of diphtheria toxin-antitoxin we became aware of the sensitization to the small amount of foreign protein in the form of horse, sheep, or goat serum it contained. Then came fluid diphtheria toxoid which was followed by the alum-precipitated toxoid. These did not contain animal serums to which the individual might become sensitized, but they did contain bacterial products and other substances of an animal nature used in the broth of the culture media. While children under 9 years of age might have some slight reaction to the diphtheria toxoid, the local and constitutional reactions in adults were so severe that it was not extensively used for them. This may have been due to previous sensitization to the products of the diphtheria bacillus. Next, tetanus toxoids were developed, and they have become even more widely used in adults than in children. Staphylococcus toxoid is used some, and a pertussis toxoid is now being developed. Of the vaccines, that for pertussis has been most widely used next to smallpox. There is also some general use of typhoid, cold, and pyogenic organism vaccines.

Types of Reactions.—The manifestations of allergy or hypersensitiveness are varied both as to time of onset and the intensity and number of symptoms. It is not common for these reactions to occur after the first injection. The usual occurrence is after the second injection.

Reactions which have allergic manifestations are usually spoken of as immediate, delayed, or late, depending upon their time of onset after the injection. When there are reactions without any of the characteristic allergic symptoms, they are usually referred to as local and constitutional.

Immediate reactions are those that occur within one hour after the injection. When severe, they are often referred to as anaphylactic shock or crisis. The most severe reactions following toxoid injection fall in this group. There may be severe shock with loss of consciousness and possibly convulsions. This may be preceded by itching of the nose or body, or a tingling sensation. Then there may be fever with or without chills, cyanosis, dyspnea or varying degrees of asthma, localized or generalized urticaria, edema, abdominal pain with or without vomiting, and diarrhea, and, at times, joint pains. There is an immediate favorable response following the injection of about 5 minims of adrenalin. Death has occurred during an immediate reaction following serum injection, but I know of no such instances following toxoids or vaccines. Although severe immediate reactions have been reported in adults following toxoids, I could find only one such instance in a child. Milder reactions with only urticaria have been reported. I know of no such instances following the use of such vaccines as pertussis, typhoid, or cold. I have seen a severe exacerbation of asthma in an asthmatic patient being treated with injections of an autogenous vaccine.

The intensity and diversity of symptoms occurring during an immediate reaction are exemplified in the following cases:

1. A boy, reported by Sisson,[1] with a definite history of allergy, received his second dose of alum-precipitated tetanus toxoid three months after the first. One hour after leaving the office he could not breathe and his eyes were about closed. The mother thought he was "going to pass out of the picture." A few moments after receiving a suitable dose of adrenalin he became normal.

2. I[2] observed an urticarial reaction in a 7-year-old girl with a definite history of pollen allergy. She had a few urticarial lesions that disappeared spontaneously within an hour after her first dose of tetanus alum-precipitated toxoid. Within an hour after her second dose of the same toxoid three months later, she had a moderately severe generalized urticaria which immediately responded to an injection of 4 minims of adrenalin.

3. A male 52 years of age, reported by Whittingham,[3] had two subcutaneous injections of tetanus antitoxin (serum 1,000 units) eleven years ago. No serum

sickness followed either injection. He was given a second injection of 1 c.c. of fluid tetanus toxoid forty-four days after his first injection. One hour later he was found in a state of collapse with dyspnea, restlessness, shivering, intense general pruritus, and frequent bouts of vomiting. There was generalized edema, and the skin of the hands and fingers had a curious marblelike appearance due to patches of dead white color. Within fifteen minutes after the injection he felt his eyes getting hot, and they became bloodshot. The lips became swollen. This was followed by vomiting, diarrhea, and loss of consciousness. After he came to, he left the lavatory and collapsed again. He was given ¾ c.c. of adrenalin 1:1,000 subcutaneously, and the itching was quickly relieved. Within twenty minutes there was a remarkable general improvement. He was later skin tested, and the Witte peptone of the toxoid gave a positive reaction.

Accelerated reactions usually occur from one to twenty-four hours after the injection. The symptoms may be the same as those of an immediate reaction but are milder. Few accelerated reactions with the allergic syndrome have been reported. Those that I have found were made up of a mild urticaria or asthma and followed toxoids and not vaccines.

Late reactions may occur from twenty-four hours to two weeks after injection but are most common from the sixth to the tenth day. Usually they are manifested by fever and chills, severe urticaria, edema, adenitis, joint pains, and gastrointestinal symptoms. Although this reaction is very common after serum, it must be very uncommon following toxoids as I could find no reports in the immediate literature on late reactions with allergic symptoms from toxoids or vaccines. Jones and Moss[4] report one case of a severe local reaction occurring on the fifth day, and one local and constitutional reaction on the sixth day, both following the administration of tetanus toxoid.

Local and constitutional reactions which may follow the administration of toxoids and vaccines are considered by many to be of an allergic nature although not accompanied by the allergic syndrome. These reactions, when they appear, fall almost entirely into the same time period after injection, that is, two to twenty-four hours, as do the accelerated reactions mentioned above.

The administration of toxoids is nearly always accompanied by rather severe stinging and burning, and it is not unusual to have a nodule present from one to several weeks with alum-precipitated toxoid. Such a nodule may also be present after pertussis vaccine. Local reactions are comprised of varying degrees of swelling of the arm in the area of injection. This may be accompanied by redness of the skin, and often tenderness and pain are present. Such reactions seem to be more frequent with the combined diphtheria and tetanus alum-precipitated toxoid than with tetanus toxoid alone. They may last from a few hours to a few days. At times a sterile abscess may form at the site of inoculation as late as ten weeks after injection. Such abscesses have been reported after diphtheria alum-precipitated toxoid, but there are few reports of them following tetanus alum-precipitated toxoid. I have never encountered a sterile abscess from tetanus alum-precipitated toxoid alone or combined with diphtheria toxoid. A few reports are available on pertussis toxoid alone and combined with diphtheria toxoid. Local reactions and sterile abscesses are apparently more commonly mentioned from its use than from the use of diphtheria and tetanus toxoids. Mild local reactions are not uncommon with pertussis vaccines. With the other vaccines the amount of local reaction seems to depend a great deal on the size of the dose used.

Constitutional reactions usually last from a few hours to a few days. The symptoms may be mild with only slight malaise, or there may be malaise, fever, headache, and gastrointestinal disturbances. Constitutional symptoms in children and infants are more frequent after pertussis vaccines than after the toxoids.

Incidence of Reactions.—The actual frequency of adverse reactions following the use of toxoids is difficult to determine. Individual experiences vary a great deal. Ramon[5] states that after having given thousands of injections of tetanus anatoxin (toxoid) he still has to see an untoward local or general reaction to speak of. This is in contrast to recent publications by other authors. Undoubtedly many reactions occurring in individual practices have never been reported.

The only severe immediate allergic reaction following tetanus toxoid in a child that I have been able to find in the recent literature is the patient reported by Sisson.[1] In this boy, edema of the eyes and severe dyspnea developed within one hour of the second injection of tetanus alum-precipitated toxoid. Immediate recovery followed the injection of adrenalin.

Peshkin[6] immunized 186 allergic children, using two or more injections of combined diphtheria and tetanus alum-precipitated toxoid. He reports that 25 per cent had local reactions of varying degree about equally frequent after the first and subsequent injections. None developed a sterile abscess. In only two children did a systemic reaction with fever occur. No reaction resembled in any way the known allergic syndrome.

In the 600 infants given 1,500 injections of diphtheria and tetanus alum-precipitated toxoid by Deamer,[7] local reactions occurred but were not troublesome. In general they compared to those following Sauer's pertussis vaccine. In a smaller number of older children sterile abscesses developed in two 7-year-old girls. General reactions were very few. There were two instances of mild urticaria an hour or two after the injection, and in one other child a mild asthmatic attack occurred four hours after an injection. In all three cases similar symptoms had occurred previous to any injection.

Unger[8] gave tetanus toxoid to 171 allergic individuals with local reactions in 7.9 per cent. In this group there were twenty-three children with local reactions in about 23 per cent. In none of the whole group did allergic or systemic reactions occur.

McBryde[9] injected ninety-four colored children with two doses of tetanus alum-precipitated toxoid. Less than 10 per cent of the children complained of slight local reactions. He does not mention any allergic reactions, and in no child was there a definite febrile reaction.

In my own experience with diphtheria and tetanus toxoids, both fluid and alum-precipitated, I have encountered no immediate severe allergic reactions in approximately 2,500 injections in infants and children. Local reactions followed in less than 10 per cent of the cases. They were somewhat more frequent following alum-precipitated toxoid than following fluid toxoid. In no instance did a sterile abscess occur. Urticaria developed in two children within one hour after injection. In one the urticaria appeared after both the first and second injections of alum-precipitated toxoid. In the other it occurred after the first injection of combined diphtheria and tetanus alum-precipitated toxoid but not after the second injection. In only four instances did a febrile reaction occur. Two of these children had a fever of 102° F. due to a throat infection at the time of injection of the combined diphtheria and tetanus toxoid. After the injection the temperature rose to 105° F. In the two other children the temperature subsided after about twelve hours.

Whittingham,[3] in reporting his experience with fluid tetanus toxoid in the British Army, gives an incidence of 651 or 1.06 per cent local reactions occurring in 61,042 adults. Fourteen, or 0.023 per cent, had definite constitutional reactions after the second injection. Of these, nine had some urticaria. There were two patients, or 1 in 30,521, who had an immediate anaphylactic crisis from which they recovered following the use of adrenalin.

Of 300 adults, reported by Parish and Oakley,[10] who received two injections of tetanus fluid toxoid, anaphylactic shock with recovery occurred in one.

Cunningham[11] reports the case of a nurse who had a severe allergic reaction three weeks after the first injection of tetanus fluid toxoid. Six weeks after the first injection she was given the second preceded by an injection of adrenalin. Within five minutes she developed a severe anaphylactic reaction from which she recovered.

One instance of severe immediate reaction is reported by Cooke[12] in only twenty-five reinjections of tetanus toxoid in adults. There was a rapid recovery. There was also one local reaction. He mentions two cases with urticaria on the second day, one following the second injection, and one the third injection.

Gold[13] has given 1,000 injections of alum-precipitated toxoid and has only had one systemic reaction with urticaria. This happened after a second injection. He also collected from the literature the reports on 1,700 patients who were immunized with two injections of tetanus alum-precipitated toxoid. There were only two instances of urticaria in this group.

Hall[14] reports fifty reactions from tetanus alum toxoid in 1,800 people, thirty-eight of whom had sore arms. There were some instances of fever and malaise. Four patients had urticaria. Anaphylactic shock occurred in one instance. Upon changing to another lot of toxoid there were no further reactions.

The above reports are typical of those in the literature on tetanus and diphtheria toxoid. Severe allergic reactions are extremely rare in children and only slightly more frequent in adults. Mild urticarial reactions, although they occur occasionally, are not troublesome. It seems that fluid toxoid produces more reactions than does alum-precipitated toxoid. This may be due to the fact that as we grow older we become more sensitive to proteins, and that an antigen in fluid form, because it is absorbed more rapidly, will produce more reactions. Deep injections also seem to produce less local reaction than do more superficial ones.

Of the vaccines, pertussis is undoubtedly the one most widely used. Local reactions occur, but they are usually mild and not troublesome. Constitutional reactions with fever are more frequent and severe than with diphtheria and tetanus toxoids. I have been unable to find any reports that allergic reactions followed the use of standard pertussis vaccine. Recently pertussis fluid toxoid and alum-precipitated toxoid alone or with diphtheria toxoid have been developed. The local reactions following their use seem to be more severe than with tetanus and diphtheria toxoids. Sterile abscesses seem to occur frequently. One physician informed me that he has seen as many as fifteen sterile abscesses with a pertussis toxoid. Kendrick[15] reports one sterile abscess in 655 children receiving alum-precipitated pertussis toxoid, and three sterile abscesses in 900 children receiving combined pertussis and diphtheria alum-precipitated toxoid. Possibly future refinements will decrease the incidence of sterile abscess formation.

Although local and constitutional reactions occur with typhoid vaccines, I know of no reactions with the allergic syndrome. This is also the case with staphylococcus toxoid and other bacterial vaccines. Reactions with these materials are easily controlled by the dosage.

Intracutaneous or intradermal injection of both toxoids and vaccines is gradually gaining in popularity. In general, there is much less local and constitutional reaction than with subcutaneous injections. Allergic reactions should also be less frequent and severe. We[16] have used intradermal injections of diphtheria and tetanus toxoids, alone and combined, in both the fluid and alum-precipitated form in over fifty allergic children and have seen no local, constitutional, or allergic reactions. There was no abscess formation.

Skin Tests With Toxoids and Their Constituents.—Toxoids contain bacterial products, broth, preservatives, formaldehyde, and alum, while the vaccines usually contain only bacterial products and preservatives. The broth or media on which the cultures for toxoids are grown usually contain beef or veal extract or infusion

and, most commonly, Witte or Berma peptones. Other peptones that may be used are Difco and Bactopeptone. Witte peptone, for example, contains beef and pork fibrin. It has been definitely established by skin scratch tests and passive transfer tests that sensitization to the peptones is fairly common. Sensitization may also occur to bacterial products.

Neil and Fleming[17] have shown that induced sensitiveness to the bacterial products of the diphtheria bacillus occurs. Cooke[12] demonstrated in one case sensitization to the products of *Clostridium tetani* in the tetanus toxoid after the second injection.

Cooke[12] reported four instances of sensitization to tetanus toxoid in twenty-five reinjections. There was a positive test with the tetanus toxoid in a 23-year-old patient who had an immediate allergic reaction following the second dose of tetanus toxoid. Precipitin tests of the patient's blood were negative with Berma peptone and with the broth media used in making the toxoid. Passive transfer tests of the patient's serum with several brands of tetanus toxoid and the ingredients of the toxoids were done. Positive tests were recorded for the alum-precipitated tetanus toxoid used, broth of the toxoid, Berma peptone, Witte peptone, two other commercial toxoids, and a suggestive reaction to one other toxoid. The tests were negative with Bactopeptone, veal infusion, beef infusion, alum, 0.4 per cent; merthiolate, 0.01 per cent; formaldehyde, 0.005 per cent; and dextrose, 1 per cent. In a second case the scratch test to tetanus toxoid before the second injection was so positive that the second injection was not given. Later the skin test and the passive transfer test became negative. The injection was then given and no reaction occurred. In a third case with mild allergic symptoms, immediately after the second injection, the scratch test was very positive for tetanus toxoid. In the fourth case, although there was no reaction following the second injection, the passive transfer tests were positive with the tetanus toxoid and Berma peptone. They also report two cases in which urticaria developed after a second injection in one and a third injection in the other, although there was no significant skin test reaction before or after the injections.

Parish and Oakley,[10] Whittingham,[3] and Cunningham[11] did skin tests on four patients who had a severe anaphylactic crisis, on three who had constitutional reactions, and on five with no reactions after the second injections of fluid tetanus toxoid. The skin tests were positive for Witte peptone used in the toxoid but negative for beef extract in all patients whether or not they had had a reaction.

Gold[13] did skin tests with two brands of tetanus toxoid as well as with various peptones and broths used in their manufacture. Seven individuals tested before they received injections of tetanus toxoid all gave negative skin tests. Of forty tested one to six months after the first injection, twenty had positive skin tests to one or more of the above materials. Gold found that Berma peptone sensitizes more frequently than does Difco peptone. He also found that there was no correlation between positive skin tests and reactions.

Peshkin[6] did skin tests with undiluted tetanus alum-precipitated toxoid on 114 children from two to thirty months after their second injection of toxoid. All gave negative reactions to the scratch test. He also tested thirty-six children after the third and fourth injections, and all were negative although many of them had had local reactions.

Comment.—Hypersensitization to toxoids and vaccines is a very individual process. It may occur naturally, but it most frequently occurs after the first injection. It may disappear after a few months or may last for years. Although it does occur with bacterial products, it usually is caused by peptone, most frequently the Witte and Berma. In a recent communication I received from one of the commercial firms, the writer stated that the Government has instructed all laboratories supplying the Army to discontinue the use of Berma and Witte peptones. Since this

change he did not believe that there had been any reduction in the number of reactions, however. Sensitization as demonstrated by the skin test and passive transfer test does not seem to bear a close relationship to the frequency of allergic reactions. Many individuals who have received tetanus toxoid give a positive skin test without having had any untoward reaction from the toxoid. Others with negative skin tests may have allergic reactions. In children negative skin tests are apparently the usual thing whether or not reactions occur. There is no relationship between pollen, contact, and food allergy and the reactions following toxoids. From a review of the present known facts there would seem to be little practical value in doing routine skin tests with toxoids and vaccines. This would only make a simple procedure cumbersome. Although a few of the immediate allergic reactions have been severe, especially in adults, I know of no instance of one having been fatal. One should keep in mind that such reactions may occur.

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REPORT OF THE TREASURER

Statement of Receipts and Disbursements

July 1, 1942 to June 30, 1943

Balance in checking account, July 1, 1942			$ 1,913.39
Balance in savings account, Initiation fees			5,703.85
Balance in savings account, International Congress			500.00
			$ 8,117.24
Receipts:			
Dues		$26,693.33	
Exhibits, 1942 meeting		2,860.00	
Initiation fees		2,225.00	
Interest earned		789.52	
Pamphlets			
Child Health Record	$ 415.90		
Immunization Procedures	405.85		
Vitamins	6.90	828.65	
Subscription (Men in service)		322.92	
Pan-American Child Congress (Refund)		4,715.62	$38,435.04
			$46,552.28
Disbursements:			
Annual meeting, 1942		$ 4,137.20	
Bank charge and exchange		155.31	
Certificates and mounting		134.85	
Executive board		2,419.34	
Miscellaneous		149.16	
Office supplies and equipment		194.06	
Postage		542.35	
Publicity		1,609.46	
Refunds (Initiation fee)		100.00	
Rent		1,200.00	
Salaries			
Secretary	$8,100.00		
Assistant secretary	1,300.00		
Stenographer	2,080.00		
Office	1,034.50	12,514.50*	
Stationery and printing		1,154.10	
Subscriptions		6,789.08	
Telephone and telegram		332.71	
Travel expense (Secretary)		153.06	
Treasurer's bond		87.50	
Expense of			
Regions		1,135.64	
States		200.21	
Committees		298.49	
Pamphlets			
Child Health Record	$ 336.80		
Immunization Procedures	699.93		
Vitamins	.81	$ 1,037.54	$34,347.56
Balance, June 30, 1943			$12,204.72
Balance in checking account, June 30, 1943			3,679.11
Balance in savings account, initiation fees			8,018.08
Balance in savings account, International Congress			507.53
			$12,204.72

*The reason for the increase in this item is a matter of bookkeeping. Salaries are now being paid at the end of the month instead of the first of the month following service.

News and Notes

Written examinations for candidates appearing before the American Board of Pediatrics will be held on Oct. 8, 1943. Instructions to candidates for the examination will be issued from the office of the secretary in due time.

Oral examinations will be conducted by the Board in New York City on Nov. 20-21, 1943, and in Cincinnati, Ohio, on Dec. 11, 1943.

The following men have been elected to membership in the American Academy of Pediatrics, Region V.

Colombia, S. A.:

Dr. Jorge Bejarano, Calle 16 N 10-09, Bogotá.
Dr. Rafael Barberi Cualla, Carrera 10 #7-71, Bogotá.
Dr. Rubén Gamboa Echandía, Ibagué. (T) Carrera 2a-#11-13.
Dr. Jorge Camacho Gamba, Apartado No. 635, Bogotá.
Dr. Hector Pedraza, Calle 43 No. 8-80, Bogotá.
Dr. Calixto Torres-Umaña, Calle 16 No. 4-66, Bogotá.
Dr. Eustacio de Mendoza Vargas, Calle 37, No. 13-44, Bogotá.

Salvador, C. A.:

Dr. Panulfo Castro, 4a Calle Oriente No. 88, San Salvador.

The deaths of three members of the Academy have been reported:

Dr. Leonard F. Bender, Philadelphia, Pa., June 8, 1943.
Dr. J. Gibson Logue, Williamsport, Pa., March 26, 1943.
Dr. John A. Schoonover, Denver, Colo., July 13, 1943.

Book Reviews

Births, Infant Mortality, Maternal Mortality, 1940. Graphic Presentation. U. S. Department of Labor, Children's Bureau, Publication 288, Washington, D. C., 1943.

A volume of thirty-four full-page graphs based on data released by the U. S. Bureau of the Census for 1940. This is one of the best graphic presentations of the subject the reviewer has seen. The material as to age, race, geographic distribution of births and of infant and maternal deaths for 1940 is presented clearly and adequately. This is the last series that will be issued for the duration of the war. It is invaluable material for pediatricians and public health workers.

Facts About Crippled Children. U. S. Department of Labor, Children's Bureau, Publication 293, 14 pages.

A discussion of the number of crippled children, causes, the work of public agencies and the Federal Government program. Full information as to state programs and the administration of federal funds is included.

Facts About Child Health. U. S. Department of Labor, Children's Bureau, Publication 294, Washington, D. C., 1943.

A fifteen-page bulletin presenting certain factual information as regards the number of children in the United States, birth rates, and distribution of the child population. To this is added information as to health needs and the means for meeting the needs. This is followed by a discussion of how well the needs are being met and wartime problems.